Scientific and Technical Information Center

SEARCH REQUEST FORM

Requester's Full Name: _____ Examiner # : _____ Date: 2/24/09

Art Unit: _____ Phone Number: 2-_____ Serial Number: 10/522,505

Location (Bldg/Room#): _____ Mailbox #: _____ Results Format Preferred (circle): PAPER DISK

****

To ensure an efficient and quality search, please attach a copy of the cover sheet, claims, and abstract or fill out the following:

Title of Invention: Method for Synthesis of Anthracycline Peptide Conjugates

Inventors (please provide full names): See attached Bib sheet

Earliest Priority Date: See attached Bib Sheet

Search Topic:

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known.

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

(1) Please search the generic of making the compound of Formula (I) in claim 1 - see claim 10 too

(2) Please search the compound in claim 14

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=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 12:48:18 ON 04 MAR 2009
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE COVERS 1907 - 4 Mar 2009  VOL 150 ISS 10
FILE LAST UPDATED: 3 Mar 2009  (20090303/ED)

HCAplus now includes complete International Patent Classification (IPC)
reclassification data for the third quarter of 2008.
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CAS Information Use Policies apply and are available at:

http://www.cas.org/legal/infopolicy.html

This file contains CAS Registry Numbers for easy and accurate substance identification.

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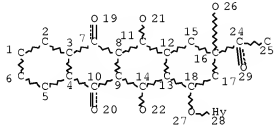

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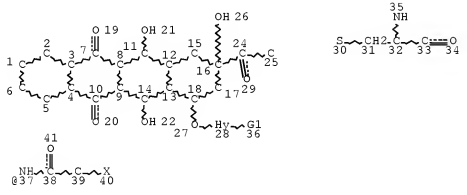

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L13  ANSWER 1 OF 2  HCAPLUS  COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER:         2006:1061789  HCAPLUS  Full-text
DOCUMENT NUMBER:          146:49894
TITLE:                    Improved Therapeutic Efficacy of Doxorubicin through
                          Conjugation with a Novel Peptide Drug Delivery
                          Technology (Vectocell)
AUTHOR(S):                Meyer-Losic, Florence; Quinonero, Jerome; Dubois,
                          Vincent; Alluis, Bertrand; Dechambre, Mireille;
                          Michel, Matthieu; Cailler, Francoise; Fernandez,
                          Anne-Marie; Trouet, Andre; Kearsey, Jonathan
CORPORATE SOURCE:         Diatos S.A., Paris, 75014, Fr.
SOURCE:                   Journal of Medicinal Chemistry (2006), 49(23),
                          6908-6916
                          CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER:                American Chemical Society
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
OTHER SOURCE(S):          CASREACT 146:49894
AB    Improvement in the therapeutic index of doxorubicin, a cytotoxic mol., has
      been sought through its chemical conjugation to short (15-23 amino acid)
      peptide sequences called Vectocell peptides.  Vectocell peptides are highly
      charged drug delivery peptides and display a number of characteristics that
      make them attractive candidates to minimize many of the limitations observed
      for a broad range of cytotoxic mols.  The studies reported here characterized
      the in vitro and in vivo efficacy of a range of Vectocell peptides conjugated
      to doxorubicin through different linkers.  These studies show that the in vivo
      therapeutic index of doxorubicin can be improved by conjugation with a
      specific Vectocell peptide (DPV1047) through an ester linker to C14 of
      doxorubicin, in both colon and breast tumor models.  This conjugate was also
      shown to have significant in vivo antitumoral activity in a model resistant to
      doxorubicin, suggesting that this conjugate is able to circumvent the
      multidrug resistance (MDR) phenotype.  These expts. therefore provide support
      for the use of the Vectocell technol. with other cytotoxic agents.
IT    916443-75-9P
      RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological
      activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL
      (Biological study); PREP (Preparation); USES (Uses)
         (improved therapeutic efficacy of doxorubicin through conjugation with
         peptides using drug delivery technol. Vectocell)
RN    916443-75-9  HCAPLUS
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      dioxo-2-naphthacenyl]-2-oxoethoxy]-4-oxobutyl]-2,5-dioxo-3-pyrrolidinyl]-L-
      cysteinyl-L-valyl-L-lysyl-L-arginylglycyl-L-leucyl-L-lysyl-L-leucyl-L-
      arginyl-L-histidyl-L-valyl-L-arginyl-L-prolyl-L-arginyl-L-valyl-L-threonyl-
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Absolute stereochemistry.
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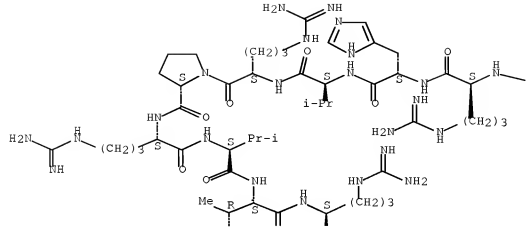

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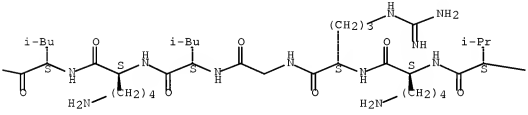

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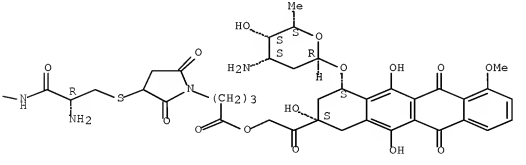

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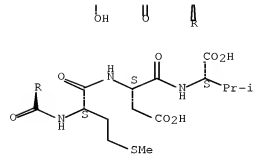

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916443-81-7P
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(improved therapeutic efficacy of doxorubicin through conjugation with peptides using drug delivery technol. Vectocell)
RN 916443-68-0 HCAPLUS
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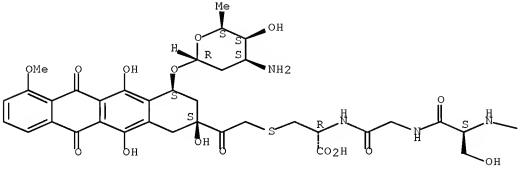
Absolute stereochemistry.

PAGE 1-A



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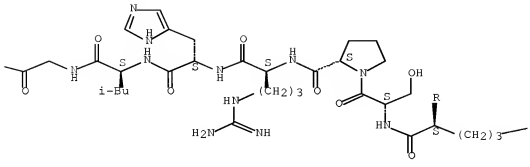

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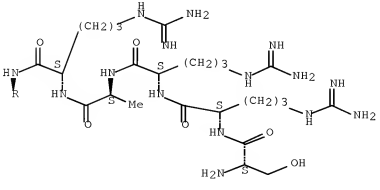

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Absolute stereochemistry.

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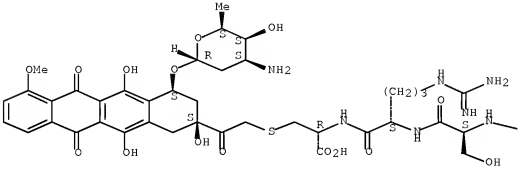

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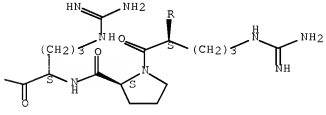

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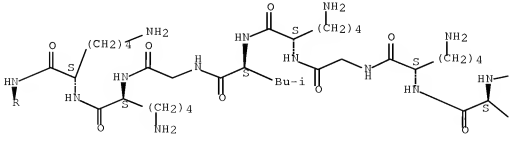

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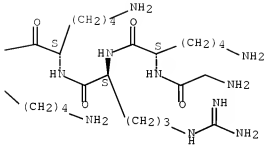

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Absolute stereochemistry.

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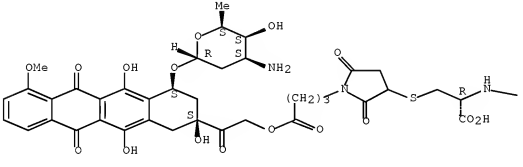

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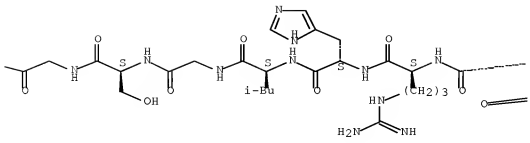

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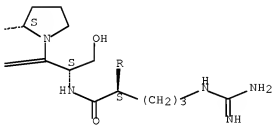

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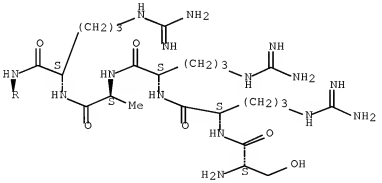

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Absolute stereochemistry.

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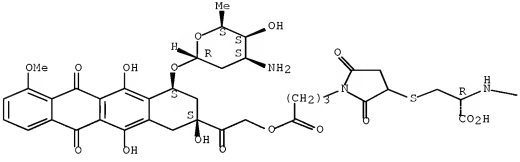

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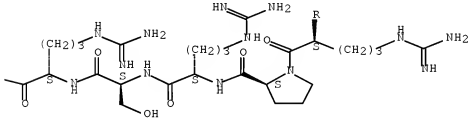

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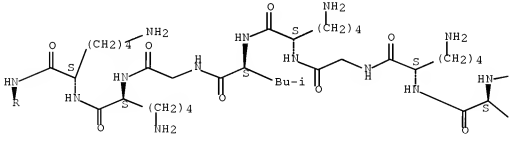

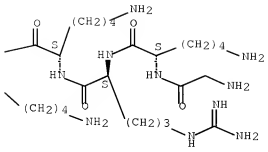

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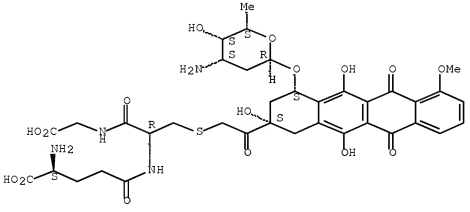
L13 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1998:429223 HCAPLUS Full-text
DOCUMENT NUMBER: 129:170191
ORIGINAL REFERENCE NO.: 129:34424h,34425a
TITLE: Doxorubicin- and daunorubicin-glutathione conjugates, but not unconjugated drugs, competitively inhibit leukotriene C4 transport mediated by MRP/GS-X pump
AUTHOR(S): Prieb, Waldemar; Krawczyk, Marta; Kuo, M. Tien; Yamane, Yoshiaki; Savaraj, Niramol; Ishikawa, Toshihisa
CORPORATE SOURCE: Department of Bioimmunotherapy, Department of Molecular Pathology, Department of Experimental Pediatrics, Univ. of Texas M. D. Anderson Cancer Center, Houston, TX, 77030, USA
SOURCE: Biochemical and Biophysical Research Communications (1998), 247(3), 859-863
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Overexpression of the multidrug resistance-associated protein (MRP1) gene encoding a human GS-X pump in cultured cells resulted in increased cellular resistance to antitumor agents, including doxorubicin (Dox) and daunomycin (Dau), as well as certain heavy metals. However, studies with membrane vesicles prepared from the resistant cells revealed that Dox and Dau are poor substrates for the transport mediated by MRP/GS-X pump, suggesting that metabolic modifications of these drugs might be required for the transport. To test this hypothesis, we prepared four glutathione conjugates by linking the cysteine residue of GSH to Dox and Dau at either the C-7 or C-14 position. The affinity of the synthesized conjugates toward MRP/GS-X pump was examined in the LTC4 transport assay using membrane vesicles prepared from an MRP1 gene-overexpressing cell line, SR3A. Unconjugated Dox and Dau failed to inhibit the transport of LTC4, whereas 30 μM GS-Dox or GS-Dau conjugates completely inhibited the transport. Kinetic analyses revealed that the inhibition by these GS-conjugates is competitive with Ki values ranging from 60 to 200 nM, suggesting that these compds. have high affinities toward MRP/GS-X pump and share the common binding site(s) with LTC4. Our present results support the hypothesis that glutathionation can facilitate the transport of anthracyclines by the MRP/GS-X pump. (c) 1998 Academic Press.

IT 211633-53-3, WP 813
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(doxorubicin- and daunorubicin-glutathione conjugates competitively inhibit leukotriene C4 transport mediated by MRP/GS-X pump)
RN 211633-53-3 HCAPLUS
CN Glycine, L-γ-glutamyl-S-[2-[(2S,4S)-4-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-1,2,3,4,6,11-hexahydro-2,5,12-trihydroxy-7-methoxy-6,11-dioxo-2-naphthacenyl]-2-oxoethyl]-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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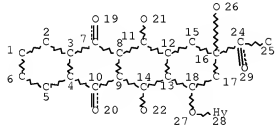

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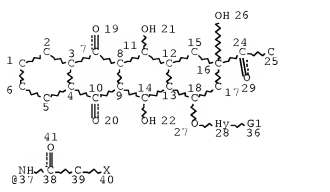

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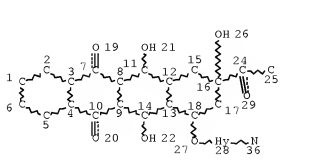

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L26        2244 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L23
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L28  ANSWER 1 OF 9  HCAPLUS  COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER:         2008:1127032  HCAPLUS  Full-text
DOCUMENT NUMBER:          149:379040
TITLE:                    Preparation of binding ligand-linked drug delivery
                          conjugates of tubulysins
INVENTOR(S):              Vlahov, Iontcho Radoslavov; Leamon, Christopher Paul;
                          Wang, Yu
PATENT ASSIGNEE(S):       Endocyte, Inc., USA
SOURCE:                   PCT Int. Appl., 95pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

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             FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE,
             KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD,
             ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH,
             PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM,
             TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
         RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU,
             IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK,
             TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD,
             TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW,
             AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
PRIORITY APPLN. INFO.:                       US 2007-894901P     P  20070314
                                             US 2007-911551P     P  20070413
OTHER SOURCE(S):          MARPAT 149:379040
GI


* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY -  AVAILABLE VIA OFFLINE PRINT *
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AB The invention relates to drug delivery conjugates B-L-D (B is a drug or targeting ligand, L is a releasable linker, D is a tubulysin), which includes conjugates of tubulysins and vitamin receptor binding ligands. Pharmaceutical compns. containing these conjugates are used for treating pathogenic cell populations. The conjugates include those described by formula I [n is 1-3; V is H, OH, alkoxy, acyloxy, or halo; W is H, OH, alkoxy, acyloxy, or alkyl; or CVW is carbonyl; X is H or (un)substituted alk(en)yl; Z is alkyl and Y is O or Z is alkyl or Y is alkyl or acyl and Y is absent; R1 is H, halo, nitro, carboxylate, cyano, OH, alkyl, etc. (with provisos)] or pharmaceutically-acceptable salts. Thus, tubulysin B conjugate II was prepared and its affinity for folate receptors and antitumor activity studied.

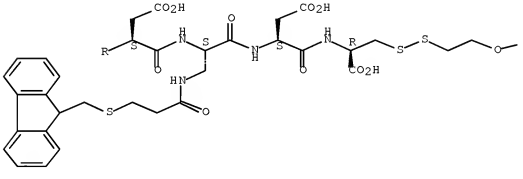
IT 1059477-98-3P, EC 0352 1059477-99-4P, EC 0358
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of binding ligand-linked drug delivery conjugates of tubulysins)

RN 1059477-98-3 HCAPLUS

CN L-Cysteine, N-[4-[[(2-amino-3,4-dihydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]-L-γ-glutamyl-L-α-aspartyl-(2S)-2-amino-3-butenoyl-L-α-aspartyl-L-α-aspartyl-3-[[3-[(9H-fluoren-9-ylmethyl)thio]-1-oxopropyl]amino]-L-alanyl-L-α-aspartyl-, disulfide with (8S,10S)-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[[(2-mercaptoethoxy)carbonyl]amino]-α-L-lyxo-hexopyranosyl]oxy]-5,12-naphthacenedione (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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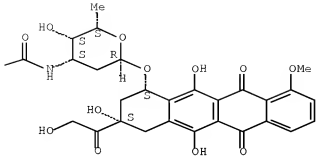

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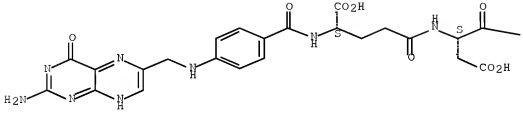

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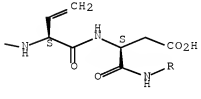
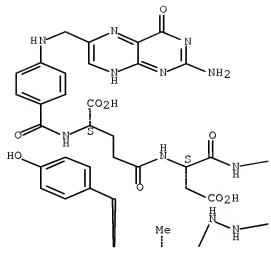


RN 1059477-99-4 HCAPLUS

CN L-Cysteine, N-[4-[[(2-amino-3,4-dihydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]-L-γ-glutamyl-L-α-aspartyl-(2S)-2-amino-3-butenoyl-L-α-asparty-L-α-aspartyl-3-[[(13S,15R)-17-[2-[(1R,3R)-1-(acetyloxy)-4-methyl-3-[[(2S,3S)-3-methyl-2-[[[(2R)-1-methyl-2-piperidinyl]carbonyl]amino]-1-oxopentyl][(1-oxobutoxy)methyl]amino]pentyl]-4-thiazolyl]-15-[(4-hydroxyphenyl)methyl]-13-methyl-1,9,12,17-tetraoxo-8-oxa-4,5-dithia-10,11,16-triazaheptadec-1-yl]amino]-L-alanyl-L-α-aspartyl-, disulfide with (8S,10S)-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[[(2-mercaptoethoxy)carbonyl]amino]-α-L-lyxo-hexopyranosyl]oxy]-5,12-naphthacenedione (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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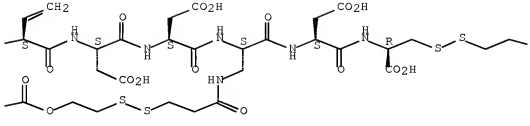
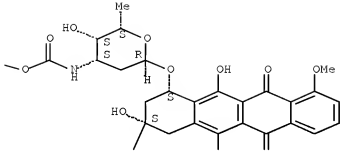


PAGE 1-C



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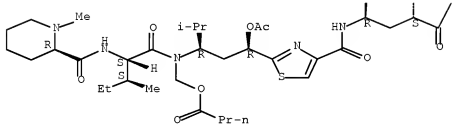


PAGE 2-C

L28 ANSWER 2 OF 9 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2008:668187 HCAPLUS Full-text
DOCUMENT NUMBER: 149:207617
TITLE: Design and synthesis of releasable folate-drug conjugates using a novel heterobifunctional disulfide-containing linker
AUTHOR(S): Satyam, Apparao
CORPORATE SOURCE: Endocyte Inc., West Lafayette, IN, 47906, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (2008), 18(11), 3196-3199
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Ltd.

DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 149:207617

AB Cellular uptake of vitamin folic acid occurs via folate-receptor mediated endocytosis. Many types of cancer cells express high levels of folate receptors as they need continuous supply of this vitamin for their proliferation. With an objective to use folic acid as a Trojan Horse' to transport anticancer drugs into cancer cells, a novel heterobifunctional disulfide-containing linker was synthesized and utilized to covalently link an amino- and hydroxyl-containing anticancer drug, and an appropriately functionalized folic acid to create novel targetable folate-drug conjugates that are shown to release free drugs under biol. relevant pH via sulfhydryl-assisted cleavage of the self-immolative disulfide-containing linker.

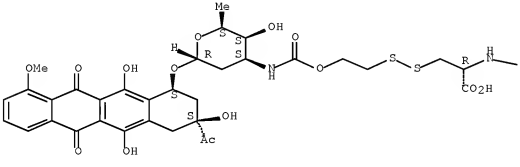
IT 742091-75-4P
RL: BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(design and synthesis of releasable folate-drug conjugates using a novel heterobifunctional disulfide-containing linker)

RN 742091-75-4 HCAPLUS

CN L-Cysteine, N-[4-[[(2-amino-1,4-dihydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]-L-γ-glutamyl-, disulfide with (8S,10S)-8-acetyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-10-[[2,3,6-trideoxy-3-[[(2-mercaptoethoxy)carbonyl]amino]-α-L-lyxo-hexopyranosyl]oxy]-5,12-naphthacenedione (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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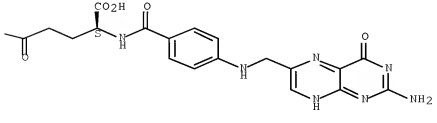
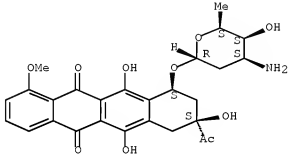


IT 20830-81-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(design and synthesis of releasable folate-drug conjugates using a novel heterobifunctional disulfide-containing linker)
RN 20830-81-3 HCAPLUS
CN 5,12-Naphthacenedione, 8-acetyl-10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 3 OF 9 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2007:619960 HCAPLUS Full-text
DOCUMENT NUMBER: 147:64501
TITLE: Inhibitors of asparaginyl endopeptidases for treatment and prevention of tumor cell invasion, metastasis and angiogenesis
INVENTOR(S): Liu, Cheng
PATENT ASSIGNEE(S): The Scripps Research Institute, USA
SOURCE: PCT Int. Appl., 224pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007064759	A2	20070607	WO 2006-US45788	20061129
WO 2007064759	A3	20080117		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH,

GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA

EP 1976861 A2 20081008 EP 2006-838642 20061129
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR

CN 101374856 A 20090225 CN 2006-80051966 20080729

PRIORITY APPLN. INFO.: US 2005-740575P P 20051129
WO 2006-US45788 W 20061129

OTHER SOURCE(S): MARPAT 147:64501

AB Derivs. of peptides with a C-terminal asparagine that can be used as inhibitors of asparaginyl endopeptidases are described for use in the diagnosis, prevention, or treatment of tumor cell invasion, metastasis and angiogenesis. For example, the invention relates to inhibitors of proteases that are specifically expressed in tumors, prodrugs activated in the tumor microenvironment and methods for using those inhibitors and prodrugs to inhibit angiogenesis and tumor cell invasion. The asparaginyl endopeptidase legumain was found to present at raised levels in a number of human tumors. Overexpression of the legumain gene in 293 cells promoted cell migration in vitro and increased the frequency of metastasis of implanted tumors in mice. A synthetic doxorubicin peptide conjugate cleavable with legumain was synthesized. The peptide was not cytotoxic to 293 cells but was profoundly cytotoxic to 293 cells overexpressing the legumain gene. It was very effective against implanted tumors in mice without adverse effects on normal tissues high in legumain.

IT 939776-59-7

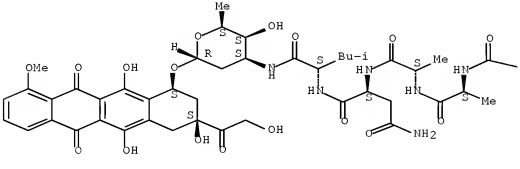
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as inhibitor of legumain; inhibitors of asparaginyl endopeptidases for treatment and prevention of tumor cell invasion, metastasis and angiogenesis)

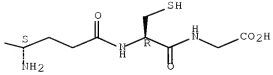
RN 939776-59-7 HCAPLUS

CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[(L-α-glutamyl-L-alanyl-L-alanyl-L-asparaginyl-L-leucyl)amino]-α-L-lyxo-hexopyranosyl]oxy]-, (1→1')-amide with L-cysteinylglycine, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



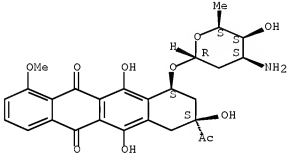


IT 20830-81-3D, Daunorubicin, conjugates with legumain substrates 58957-92-9D, conjugates with legumain substrates
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as prodrugs; inhibitors of asparaginyl endopeptidases for treatment and prevention of tumor cell invasion, metastasis and angiogenesis)

RN 20830-81-3 HCAPLUS

CN 5,12-Naphthacenedione, 8-acetyl-10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S,10S)- (CA INDEX NAME)

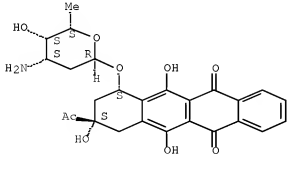
Absolute stereochemistry.



RN 58957-92-9 HCAPLUS

CN 5,12-Naphthacenedione, 9-acetyl-7-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-, (7S,9S)- (CA INDEX NAME)

Absolute stereochemistry.



L28 ANSWER 4 OF 9 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2006:1061789 HCAPLUS Full-text
DOCUMENT NUMBER: 146:49894
TITLE: Improved Therapeutic Efficacy of Doxorubicin through Conjugation with a Novel Peptide Drug Delivery Technology (Vectocell)
AUTHOR(S): Meyer-Losic, Florence; Quinonero, Jerome; Dubois, Vincent; Alluis, Bertrand; Dechambre, Mireille; Michel, Matthieu; Cailler, Francoise; Fernandez, Anne-Marie; Trouet, Andre; Kearsey, Jonathan
CORPORATE SOURCE: Diatos S.A., Paris, 75014, Fr.
SOURCE: Journal of Medicinal Chemistry (2006), 49(23), 6908-6916
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 146:49894

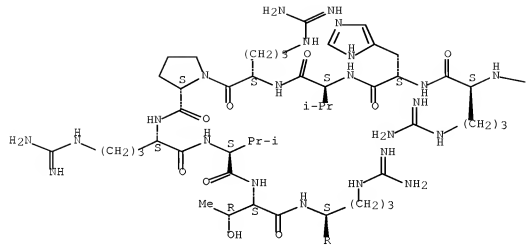
AB Improvement in the therapeutic index of doxorubicin, a cytotoxic mol., has been sought through its chemical conjugation to short (15-23 amino acid) peptide sequences called Vectocell peptides. Vectocell peptides are highly charged drug delivery peptides and display a number of characteristics that make them attractive candidates to minimize many of the limitations observed for a broad range of cytotoxic mols. The studies reported here characterized the in vitro and in vivo efficacy of a range of Vectocell peptides conjugated to doxorubicin through different linkers. These studies show that the in vivo therapeutic index of doxorubicin can be improved by conjugation with a specific Vectocell peptide (DPV1047) through an ester linker to C14 of doxorubicin, in both colon and breast tumor models. This conjugate was also shown to have significant in vivo antitumoral activity in a model resistant to doxorubicin, suggesting that this conjugate is able to circumvent the multidrug resistance (MDR) phenotype. These expts. therefore provide support for the use of the Vectocell technol. with other cytotoxic agents.

IT 916443-62-4P 916443-64-6P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(improved therapeutic efficacy of doxorubicin through conjugation with peptides using drug delivery technol. Vectocell)

RN 916443-62-4 HCAPLUS
CN L-Valine, L-cysteinyl-L-valyl-L-lysyl-L-arginylglycyl-L-leucyl-L-lysyl-L-leucyl-L-arginyl-L-histidyl-L-valyl-L-arginyl-L-prolyl-L-arginyl-L-valyl-L-threonyl-L-arginyl-L-methionyl-L-α-asparty1-, thioether with (8S,10S)-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[[4-(3-mercapto-2,5-dioxo-1-pyrrolidinyl)-1-oxobutyl]amino]-α-L-lyxo-hexopyranosyl]oxy]-5,12-naphthacenedione (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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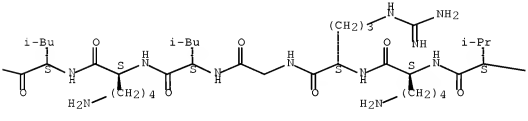
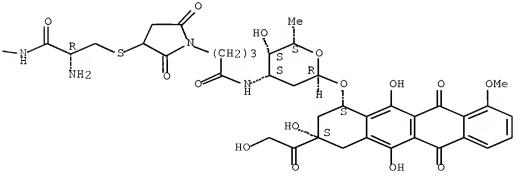


PAGE 1-C



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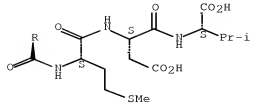
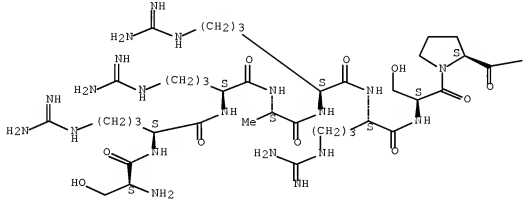


RN 916443-64-6 HCAPLUS
CN L-Cysteine, L-seryl-L-arginyl-L-arginyl-L-alanyl-L-arginyl-L-arginyl-L-seryl-L-prolyl-L-arginyl-L-histidyl-L-leucylglycyl-L-serylglycyl-, thioether with (8S,10S)-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[[4-(3-mercapto-2,5-dioxo-1-pyrrolidinyl)-1-oxobutyl]amino]-α-L-lyxo-hexopyranosyl]oxy]-5,12-naphthacenedione (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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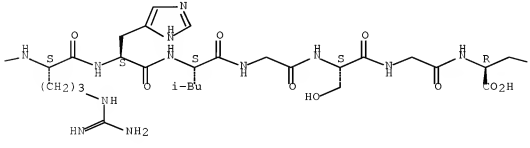
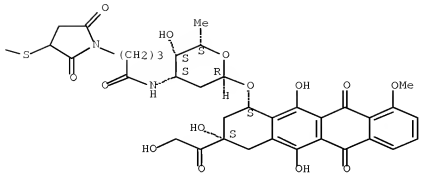




REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 5 OF 9 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:15791 HCAPLUS Full-text
DOCUMENT NUMBER: 142:120462
TITLE: Therapeutic and diagnostic conjugates for use with multispecific antibodies
INVENTOR(S): Mcbride, William J.; Goldenberg, David M.; Noren, Carl; Hansen, Hans J.
PATENT ASSIGNEE(S): Immunomedics, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 53 pp., Cont.-in-part of U.S. Ser. No. 150,654.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 20
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20050002945	A1	20050106	US 2004-776470	20040211
US 7405320	B2	20080729		
US 7074405	B1	20060711	US 1999-337756	19990622
US 7052872	B1	20060530	US 1999-382186	19990823
US 20020006379	A1	20020117	US 2001-823746	20010403
US 6962702	B2	20051108		
US 20030198595	A1	20031023	US 2002-150654	20020517
US 7138103	B2	20061121		
AU 2005211754	A1	20050825	AU 2005-211754	20050211
CA 2555666	A1	20050825	CA 2005-2555666	20050211
WO 2005077071	A2	20050825	WO 2005-US4177	20050211

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,

EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1720575 A2 20061115 EP 2005-726492 20050211

R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, LV, MK, YU

JP 2007528372 T 20071011 JP 2006-553216 20050211

PRIORITY APPLN. INFO.: US 1998-90142P P 19980622
US 1998-104156P P 19981014
US 1999-337756 A2 19990622
US 1999-382186 B2 19990823
US 2001-823746 A2 20010403
US 2002-150654 A2 20020517
US 2004-776470 A 20040211
WO 2005-US4177 W 20050211

OTHER SOURCE(S): MARPAT 142:120462

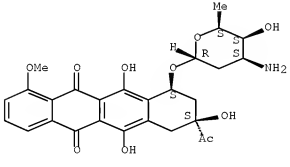
AB Disclosed are compds. that include two or more haptens conjugated by a spacer or a carrier. The haptens may include diethylenetriaminepentaacetate (DTPA), histamine-succinyl-glutamine (HSG), or combinations of DTPA and HSG. The compds. also includes an effector mol. which may be conjugated to one or more of the haptens, the spacer/carrier, or both. The effector mol. may be conjugated by a number of linkages including an ester linkage, an imino linkage, an amino linkage, a sulfide linkage, a thiosemicarbazone linkage, a semicarbazone linkage, an oxime linkage, an ether linkage, or combinations of these linkages. Also disclosed are methods of synthesizing the compds. and/or precursors of the compds.

IT 20830-81-3D, Daunorubicin, radiolabeled conjugates
58957-92-9D, Idarubicin, radiolabeled conjugates
RL: DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(therapeutic and diagnostic conjugates for use with multispecific antibodies)

RN 20830-81-3 HCAPLUS

CN 5,12-Naphthacenedione, 8-acetyl-10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S,10S)- (CA INDEX NAME)

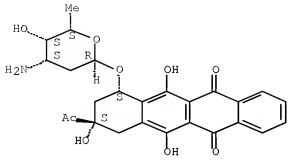
Absolute stereochemistry.



RN 58957-92-9 HCAPLUS

CN 5,12-Naphthacenedione, 9-acetyl-7-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-, (7S,9S)- (CA INDEX NAME)

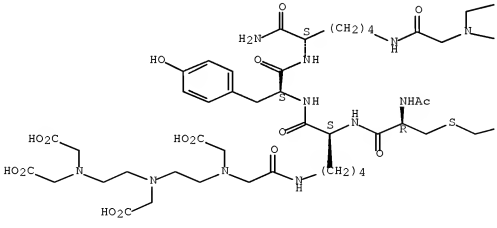
Absolute stereochemistry.



IT 819800-48-1DP, complexes with Indium
RL: DGN (Diagnostic use); PKT (Pharmacokinetics); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses)
(therapeutic and diagnostic conjugates for use with multispecific antibodies)
RN 819800-48-1 HCAPLUS
CN L-Lysinamide, N-acetyl-L-cysteinyl-N6-[N-[2-[[2-[bis(carboxymethyl)amino]ethyl](carboxymethyl)amino]ethyl]-N-(carboxymethyl)glycyl]-L-lysyl-L-tyrosyl-N6-[N-[2-[[2-[bis(carboxymethyl)amino]ethyl](carboxymethyl)amino]ethyl]-N-(carboxymethyl)glycyl]-, thioether with (8S,10S)-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[(mercaptoacetyl)amino]-α-L-lyxo-hexopyranosyl]oxy]-5,12-naphthacenedione (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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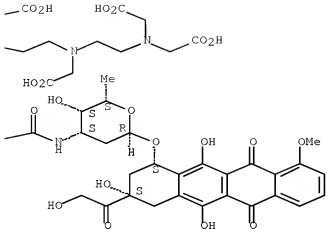
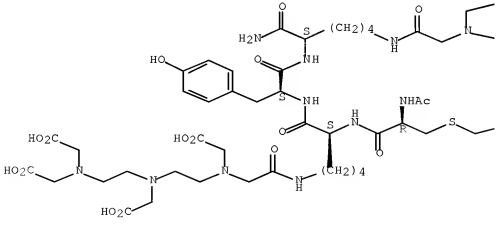
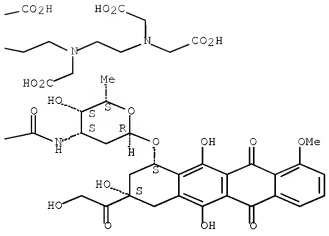


IT 819800-48-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(therapeutic and diagnostic conjugates for use with multispecific antibodies)
RN 819800-48-1 HCAPLUS
CN L-Lysinamide, N-acetyl-L-cysteinyl-N6-[N-[2-[[2-[bis(carboxymethyl)amino]ethyl](carboxymethyl)amino]ethyl]-N-(carboxymethyl)glycyl]-L-lysyl-L-tyrosyl-N6-[N-[2-[[2-[bis(carboxymethyl)amino]ethyl](carboxymethyl)amino]ethyl]-N-(carboxymethyl)glycyl]-, thioether with (8S,10S)-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[(mercaptoacetyl)amino]-α-L-lyxo-hexopyranosyl]oxy]-5,12-naphthacenedione (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A





REFERENCE COUNT: 123 THERE ARE 123 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 6 OF 9 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2004:681505 HCAPLUS Full-text
DOCUMENT NUMBER: 141:207525
TITLE: Preparation of peptide-containing vitamin receptor binding drug delivery conjugates
INVENTOR(S): Vlahov, Iontcho Radoslavov; Leamon, Christopher Paul; Parker, Matthew A.; Howard, Stephen J.; Santhapuram, Hari Krishna; Satyam, Apparao; Reddy, Joseph Anand
PATENT ASSIGNEE(S): Endocyte, Inc., USA
SOURCE: PCT Int. Appl., 110 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004069159	A2	20040819	WO 2004-US2070	20040127
WO 2004069159	A3	20050616		
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RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2004210136	A1	20040819	AU 2004-210136	20040127
CA 2512867	A1	20040819	CA 2004-2512867	20040127
US 20050002942	A1	20050106	US 2004-765336	20040127
EP 1592457	A2	20051109	EP 2004-705573	20040127

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

CN 1761488	A	20060419	CN 2004-80007679		20040127
CN 100381177	C	20080416			
JP 2006518712	T	20060817	JP 2005-518938		20040127
CN 101239190	A	20080813	CN 2008-10081563		20040127
NZ 541846	A	20081224	NZ 2004-541846		20040127
IN 2005KN01541	A	20060811	IN 2005-KN1541		20050804
PRIORITY APPLN. INFO.:			US 2003-442845P	P	20030127
			US 2003-492119P	P	20030801
			US 2003-516188P	P	20031031
			CN 2004-80007679	A3	20040127
			WO 2004-US2070	W	20040127

AB The invention describes vitamin receptor binding drug delivery conjugates and their synthesis. The drug delivery conjugate consists of a vitamin receptor binding moiety (a vitamin or vitamin receptor binding analog), a bivalent linker, and a drug or its analogs or derivs. The vitamin receptor binding moiety and the drug are covalently linked to the bivalent linker, which comprises one or more spacer linkers, releasable linkers, and heteroatom linkers. Methods and pharmaceutical compns. for eliminating pathogenic cell populations using the drug delivery conjugate are also described. Thus, a conjugate prepared from deacetylvinblastine monohydrazide, N-(4-acetylphenyl)maleimide, and folate-containing peptidyl fragment Pte-Glu-Asp-Arg-Asp-Asp-Cys-OH was effective in delaying the growth of M109 tumors in mice.

IT 742091-75-4P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

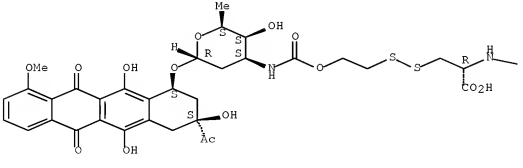
(preparation of peptide-containing vitamin receptor binding drug delivery conjugates)

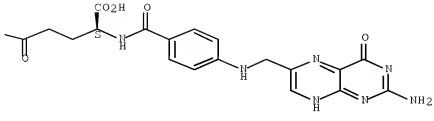
RN 742091-75-4 HCAPLUS

CN L-Cysteine, N-[4-[[(2-amino-1,4-dihydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]-L-γ-glutamyl-, disulfide with (8S,10S)-8-acetyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-10-[[2,3,6-trideoxy-3-[[(2-mercaptoethoxy)carbonyl]amino]-α-L-lyxo-hexopyranosyl]oxy]-5,12-naphthacenedione (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



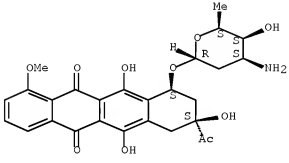


IT 20830-81-3, Daunomycin
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of peptide-containing vitamin receptor binding drug delivery conjugates)

RN 20830-81-3 HCAPLUS

CN 5,12-Naphthacenedione, 8-acetyl-10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.



L28 ANSWER 7 OF 9 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2000:34769 HCAPLUS Full-text
DOCUMENT NUMBER: 132:93654
TITLE: Preparation of peptide derivatives for improved delivery of drug therapeutic agents
INVENTOR(S): Fischer, Peter Martin; Wang, Shudong
PATENT ASSIGNEE(S): Cyclacel Limited, UK
SOURCE: PCT Int. Appl., 115 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000001417	A1	20000113	WO 1999-GB1957	19990622
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS,				

JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW

RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2333145	A1	20000113	CA 1999-2333145		19990622
CA 2333145	C	20080325			
AU 9945198	A	20000124	AU 1999-45198		19990622
AU 756014	B2	20030102			
GB 2340121	A	20000216	GB 1999-14577		19990622
GB 2340121	B	20000906			
EP 1093383	A1	20010425	EP 1999-928071		19990622
EP 1093383	B1	20041013			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
JP 2002519392	T	20020702	JP 2000-557863		19990622
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AT 279210	T	20041015	AT 1999-928071		19990622
ES 2230860	T3	20050501	ES 1999-928071		19990622
IL 140650	A	20060205	IL 1999-140650		19990622
US 6472507	B1	20021029	US 1999-346847		19990702
US 20030119735	A1	20030626	US 2002-210660		20020731
US 6992169	B2	20060131			
PRIORITY APPLN. INFO.:			GB 1998-14527	A	19980703
			WO 1999-GB1957	W	19990622
			US 1999-346847	A1	19990702

AB The present invention relates to a novel drug delivery system for use in the improved delivery of drug therapeutic agents into target cells. The system comprises a drug moiety linked to a carrier moiety wherein the carrier moiety comprises a homeobox peptide or its fragment or derivative Thus, {[4-[N-(2,4-diamino-6-pteridinylmethyl)-N-methylamino]benzoyl]-Glu- Gly-β-Ala}4-Lys2-Lys-β-Ala-Arg-Gln-Ile-Lys-Ile-Trp-Phe-Gln-Asn- Arg-Arg-Met-Lys-Trp-Lys-Lys-OH was prepared by the solid-phase method and assayed for in vitro cytotoxicity.

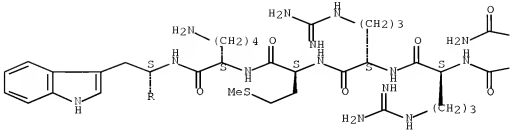
IT 254893-79-3P 254893-82-8P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of peptide derivs. for improved delivery of drug therapeutic agents)

RN 254893-79-3 HCAPLUS

CN L-Lysine, L-cysteinyl-L-arginyl-L-glutaminyl-L-isoleucyl-L-lysyl-L-isoleucyl-L-tryptophyl-L-phenylalanyl-L-glutaminyl-L-asparaginyl-L-arginyl-L-arginyl-L-methionyl-L-lysyl-L-tryptophyl-L-lysyl-, thioether with (8S,10S)-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[[3-(3-mercapto-2,5-dioxo-1-pyrrolidinyl)benzoyl]amino]-α-L-lyxo-hexopyranosyl]oxy]-5,12-naphthacenedione (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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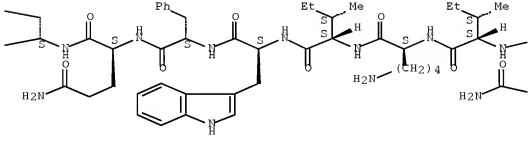

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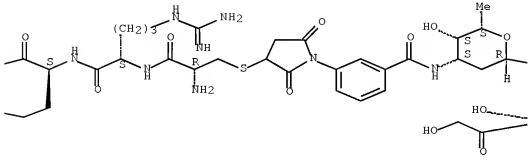

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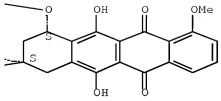

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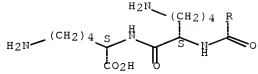
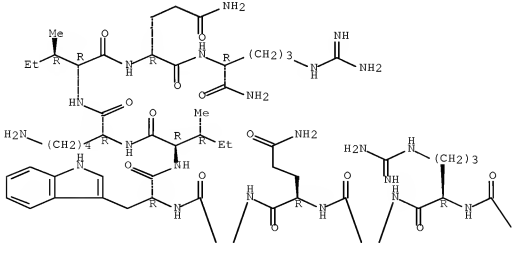


RN 254893-82-8 HCAPLUS

CN D-Argininamide, L-cysteinyl-D-lysyl-D-lysyl-D-tryptophyl-D-lysyl-D-methionyl-D-arginyl-D-arginyl-D-asparaginyl-D-glutaminyl-D-phenylalanyl-D-tryptophyl-D-isoleucyl-D-lysyl-D-isoleucyl-D-glutaminyl-, thioether with (8S,10S)-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[[3-(3-mercapto-2,5-dioxo-1-pyrrolidinyl)benzoyl]amino]-α-L-lyxo-hexopyranosyl]oxy]-5,12-naphthacenedione (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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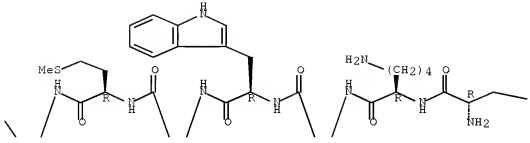

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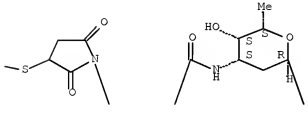

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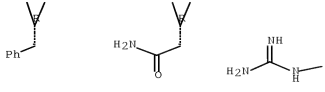

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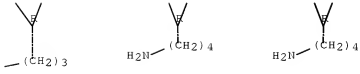

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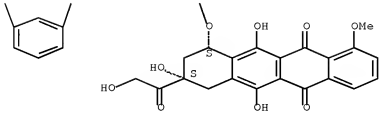
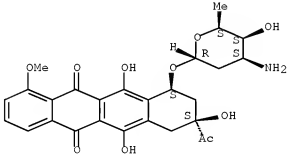


IT 20830-81-3, Daunorubicin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of peptide derivs. for improved delivery of drug therapeutic agents)

RN 20830-81-3 HCAPLUS

CN 5,12-Naphthacenedione, 8-acetyl-10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.



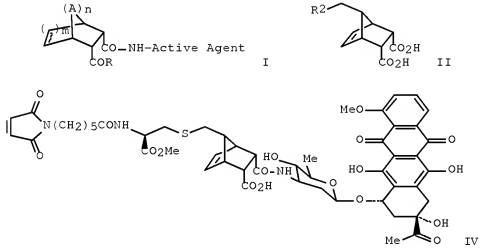
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 8 OF 9 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1999:130413 HCAPLUS Full-text
DOCUMENT NUMBER: 130:182295
TITLE: Preparation of acid-cleavable bicyclic, nonaromatic

linker agents
INVENTOR(S): Hadley, Stephen
PATENT ASSIGNEE(S): NeoRx Corporation, USA
SOURCE: U.S., 21 pp., Cont. of U.S. Ser. No. 589,579, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5874549	A	19990223	US 1993-118578	19930909
			US 1990-589579	B1 19900928

PRIORITY APPLN. INFO.:
OTHER SOURCE(S): MARPAT 130:182295
GI



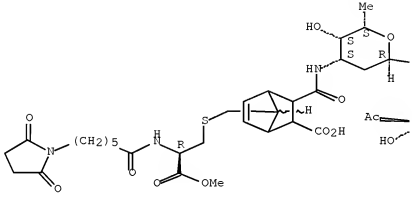
AB A bicyclic, non-aromatic hydrocarbon compound I [A = CH2, n = 1-3; A = O, S, N-C1-6 alkyl, n = 1; m = 1, 2; R = H, OR1, SR1; R1 = ester moiety; Active agent = amino group-containing therapeutic or diagnostic agent], acid-cleavably links an amide-containing active agent to a targeting agent, which is linked by a linker arm to the bicyclic skeleton. Thus, alc. II (R2 = OH) (prepared by saponification and hydrogenolysis of the corresponding benzyl ether anhydride) was converted into mesylate II (R2 = MeSO3) and reacted with Boc-Cys-OMe to give sulfide II [R2 = (R)-BocNHCH(CO2Me)CH2S] (III). Acidic deprotection of III, followed by condensation with 6-maleimidocaproyl chloride, anhydride formation with DCC, and condensation with daunomycin gave drug conjugate IV.

IT 220539-52-6P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of acid-cleavable bicyclic, nonarom. linker agents)

RN 220539-52-6 HCAPLUS
CN 5,12-Naphthacenedione, 8-acetyl-10-[[3-[[[3-carboxy-7-[[[(2R)-2-[[6-(2,5-dioxo-1-pyrrolidinyl)-1-oxohexyl]amino]-3-methoxy-3-oxopropyl]thio]methyl]bicyclo[2.2.1]hept-5-en-2-yl]carbonyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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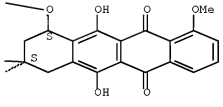
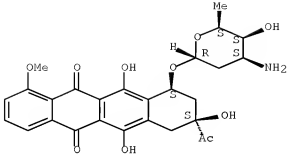


IT 20830-81-3, Daunomycin
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of acid-cleavable bicyclic, nonarom. linker agents)
RN 20830-81-3 HCAPLUS
CN 5,12-Naphthacenedione, 8-acetyl-10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 9 OF 9 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1982:417598 HCAPLUS Full-text
DOCUMENT NUMBER: 97:17598
ORIGINAL REFERENCE NO.: 97:3005a,3008a
TITLE: Biologically active conjugates of ACTH and cytotoxic drugs: properties of ACTH analogs containing daunorubicin
AUTHOR(S): Scott, D.; Ontjes, D.
CORPORATE SOURCE: Dep. Pharmacol., Univ. North Carolina, Chapel Hill, NC, 27514, USA
SOURCE: Pept.: Synth., Struct., Funct., Proc. Am. Pept. Symp., 7th (1981), 817-20. Editor(s): Rich, Daniel H.; Gross, Erhard. Pierce Chem. Co.: Rockford, Ill. CODEN: 47LMAO
DOCUMENT TYPE: Conference
LANGUAGE: English

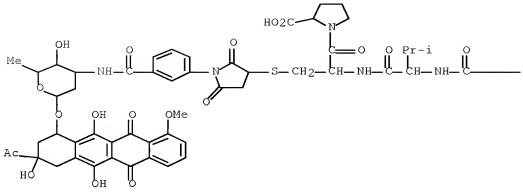
AB Daunorubicin-HCl [23541-50-6] Was conjugated to (4-norleucine, 23-cysteine)-α1-24-ACTH [82069-06-5] and to (23-cysteine)-α6-24-ACTH [82069-07-6] using m-maleimidobenzoyl N-hydroxysuccinimide ester [58626-38-3] as the coupling agent. The daunorubicin-α1-24-ACTH conjugate [82114-57-6] activated adenylate cyclase [9012-42-4] in rat adrenocortical membrane suspensions, whereas the daunorubicin-α6-24-ACTH conjugate [82069-08-7] did not. The latter conjugate lacks that part of the ACTH mol. known to mediate the steroidogenic response. Both conjugates competitively antagonized α1-24-ACTH-induced adenylate cyclase activation, indicating their ability to bind to the ACTH receptor. The daunorubicin-α1-24-ACTH conjugate significantly inhibited the growth of cultured Y-1 adrenal tumor cells.

IT 82069-08-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and adrenal cortex responses to)

RN 82069-08-7 HCAPLUS

CN α6-24-Corticotropin, 23-[S-[1-[3-[[[6-[(3-acetyl-1,2,3,4,6,11-hexahydro-3,5,12-trihydroxy-10-methoxy-6,11-dioxo-1-naphthacenyl)oxy]tetrahydro-3-hydroxy-2-methyl-2H-pyran-4-yl]amino]carbonyl]phenyl]-2,5-dioxo-3-pyrrolidinyl]-L-cysteine]- (9CI) (CA INDEX NAME)

PAGE 1-A



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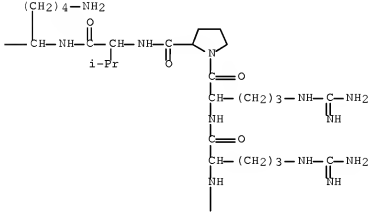

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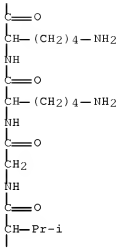

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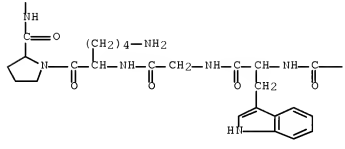

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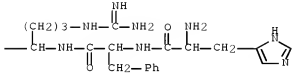

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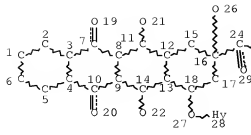

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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  28

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L11              STR
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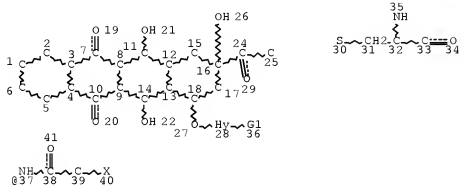

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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  40

STEREO ATTRIBUTES: NONE
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L14             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  DAUNORUBICIN/CN
L15             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  CARMINOMYCIN/CN
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L17               STR
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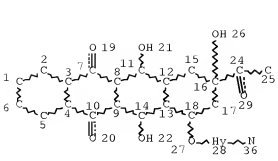

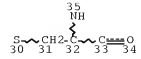

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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 35

STEREO ATTRIBUTES: NONE

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L22		SEL PLU=ON L15 1- CHEM : 4 TERMS
L23		SEL PLU=ON L16 1- CHEM : 7 TERMS
L24	9331	SEA FILE=HCAPLUS ABB=ON PLU=ON L21
L25	542	SEA FILE=HCAPLUS ABB=ON PLU=ON L22
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L29	10	SEA FILE=HCAPLUS ABB=ON PLU=ON L20 NOT (L28 OR L13)

=> d ibib abs hitstr l29 1-10

L29 ANSWER 1 OF 10 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2009:3879 HCAPLUS Full-text
DOCUMENT NUMBER: 150:93175
TITLE: Cell surface receptor-targeting ligands through hydrophilic spacer linkers to conjugate with therapeutic, diagnostic and imaging agent for disease diagnosis and therapy
INVENTOR(S): Leamon, Christopher Paul; Wang, Yu; Vlahov, Iontcho Radoslavov; You, Fei; Kleindl, Paul Joseph; Santhapuram, Hari Krishna R.
PATENT ASSIGNEE(S): Endocyte, Inc., USA
SOURCE: PCT Int. Appl., 148pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2009002993	A1	20081231	WO 2008-US68093	20080625

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2007-946092P P 20070625
US 2008-36186P P 20080313

OTHER SOURCE(S): MARPAT 150:93175

AB Described herein are compns. and methods for use in targeted drug delivery using cell- surface receptor binding drug delivery conjugates containing hydrophilic spacer linkers for use in treating disease states caused by pathogenic cell populations.

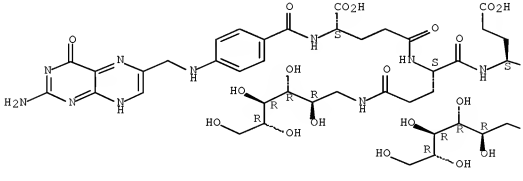
IT 1096169-25-3P
RL: BSU (Biological study, unclassified); DGN (Diagnostic use); MOA (Modifier or additive use); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(cell surface receptor-targeting ligands through hydrophilic spacer linkers to conjugate with therapeutic, diagnostic and imaging agent for disease diagnosis and therapy)

RN 1096169-25-3 HCAPLUS

CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.

PAGE 1-A



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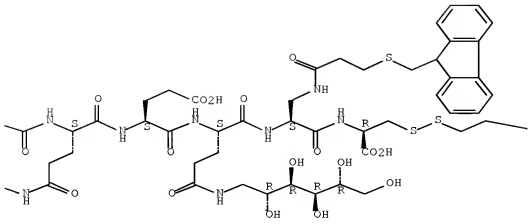

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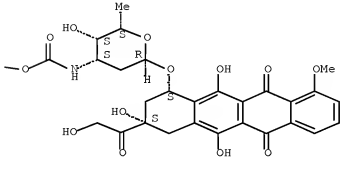


REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 2 OF 10 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2008:353245 HCAPLUS Full-text
DOCUMENT NUMBER: 148:387148
TITLE: Targeted polymeric prodrugs containing multifunctional linkers
INVENTOR(S): Zhao, Hong; Rubio, Maria Belen; Reddy, Prasanna
PATENT ASSIGNEE(S): Enzon Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 129pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2008034124	A2	20080320	WO 2007-US78600	20070915
WO 2008034124	A3	20080807		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA

PRIORITY APPLN. INFO.: US 2006-844943P P 20060915

AB The present invention provides single chain antibody-directed polymeric prodrugs containing multifunctional linkers. Methods of making the polymeric delivery systems and methods of treating mammals using the same are also disclosed. There are also provided new and advantageous compds. which employ the use of both targeting agent and PEGylation technologies as well as other improved therapeutic techniques.

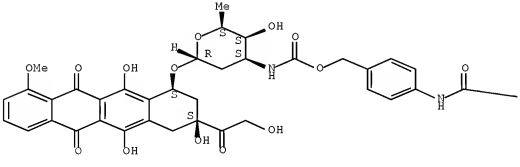
IT 1013922-38-7DP, multi-armed PEG derivative
RL: IMF (Industrial manufacture); RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)
(manufacture of targeted polymeric prodrugs containing multifunctional linkers
and use)

RN 1013922-38-7 HCAPLUS

CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[[[[4-[[N6-[N-[(1,1-dimethylethoxy)carbonyl]-3-[(3-nitro-2-pyridinyl)dithio]-L-alanyl]-L-lysyl-L-valyl-N5-(aminocarbonyl)-L-ornithyl]amino]phenyl]methoxy]carbonyl]amino]-α-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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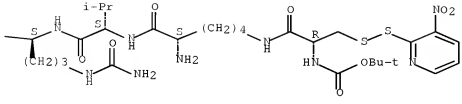


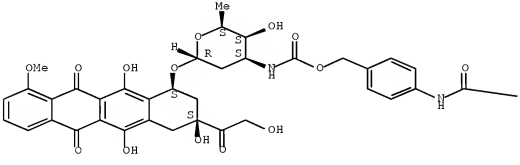
IT 1013922-41-2DP, multi-armed PEG derivative, reaction products with peptides
RL: IMF (Industrial manufacture); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(manufacture of targeted polymeric prodrugs containing multifunctional linkers and use)

RN 1013922-41-2 HCAPLUS

CN Cyclo(L-arginylglycyl-L-α-aspartyl-L-phenylalanyl-L-cysteinyl), (5→1')-disulfide with (8S,10S)-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[[[[4-[[N6-[N-[(1,1-dimethylethoxy)carbonyl]-L-cysteinyl]-L-lysyl-L-valyl-N5-(aminocarbonyl)-L-ornithyl]amino]phenyl]methoxy]carbonyl]amino]-α-L-lyxo-hexopyranosyl]oxy]-5,12-naphthacenedione (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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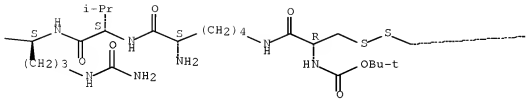

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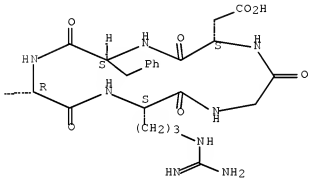

L29 ANSWER 3 OF 10 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2006:101934 HCAPLUS Full-text
DOCUMENT NUMBER: 144:171263
TITLE: Preparation of bivalent linkers for drug-peptide and other conjugates
INVENTOR(S): Vlahov, Iontcho Radoslavov; Leamon, Christopher Paul; Satyam, Apparao; Howard, Stephen, J.
PATENT ASSIGNEE(S): Endocyte, Inc., USA
SOURCE: PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006012527	A1	20060202	WO 2005-US26068	20050722

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NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

EP 1789391 A1 20070530 EP 2005-773389 20050722

R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR

CN 101098854 A 20080102 CN 2005-80031404 20050722

JP 2008507560 T 20080313 JP 2007-522811 20050722

IN 2007KN00444 A 20070706 IN 2007-KN444 20070207

PRIORITY APPLN. INFO.: US 2004-590580P P 20040723

WO 2005-US26068 W 20050722

AB The invention relates to divalent linkers derived from compds. X1-S-X-(CH2)nO2C-X2 [X is CRaRb (Ra, Rb are independently H, alkyl or CRaRb is carbocyclyl), o- or p-phenylene; n is 1-4; X1, X2 are leaving groups which are displaceable by a nucleophile, i.e., a drug, vitamin, imaging agent, diagnostic agent, or another bivalent linker], which are used to prepare conjugates with vitamins, drugs, diagnostic agents and/or imaging agents. Thus, 6-(trifluoromethyl)-1-[2-(2-pyridinyldithio)ethoxycarbonyloxy]benzotriazole was prepared and treated with a drug in the presence of N,N-dimethylaminopyridine to form the pyridyldithio-derivatized drug, which was reacted with a peptide to form the conjugate.

IT 874302-89-3P

RL: DGN (Diagnostic use); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

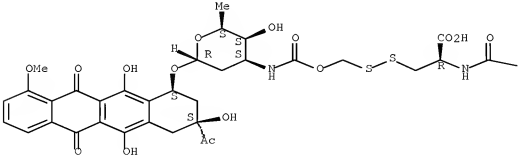
(preparation of bivalent linkers for drug-peptide and other conjugates)

RN 874302-89-3 HCAPLUS

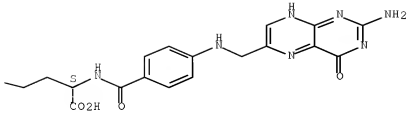
CN D-Alanine, N-[4-[[(2-amino-1,4-dihydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]-L-γ-glutamyl-3-[(hydroxymethyl)dithio]-, (1→103)-ester with (8S,10S)-8-acetyl-10-[[3-(carboxyamino)-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 4 OF 10 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:1241397 HCAPLUS Full-text
DOCUMENT NUMBER: 144:88489
TITLE: The design, synthesis, and evaluation of two universal doxorubicin-linkers: Preparation of conjugates that retain topoisomerase II activity
AUTHOR(S): Sun, Chengzao; Aspland, Simon E.; Ballatore, Carlo; Castillo, Rosario; Smith, Amos B.; Castellino, Angelo J.
CORPORATE SOURCE: Acidophil, LLC, San Diego, CA, 92121, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (2006), 16(1), 104-107
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 144:88489

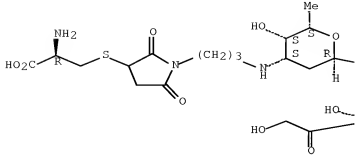
AB The design, synthesis, and evaluation of two N-alkyl-maleimide aldehydes have been achieved, which upon reductive alkylation with the C3'-amino group of doxorubicin (DOX) permits the preparation of DOX conjugates via Michael addition of thiol-containing vectors. This method enables the mild, facile, and high-throughput preparation of DOX conjugates that retain the basic C3'-nitrogen, a pre-requisite for topoisomerase II inhibition. Seven DOX-amino acid conjugates were prepared, each displaying similar inhibitory activity as the parent drug.

IT 872356-60-0P 872356-64-4P
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of doxorubicin-linker conjugates that retain topoisomerase II activity via reductive alkylation and Michael addition reactions)

RN 872356-60-0 HCAPLUS
CN 5,12-Naphthacenedione, 10-[[3-[[3-[3-[[(2R)-2-amino-2-carboxyethyl]thio]-2,5-dioxo-1-pyrrolidinyl]propyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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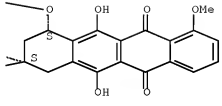
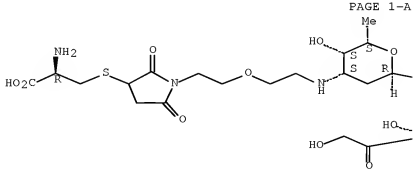
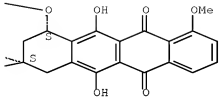


RN 872356-64-4 HCAPLUS
CN 5,12-Naphthacenedione, 10-[[3-[[2-[2-[3-[[(2R)-2-amino-2-carboxyethyl]thio]-2,5-dioxo-1-pyrrolidinyl]ethoxy]ethyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A





REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 5 OF 10 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:1084939 HCAPLUS Full-text
DOCUMENT NUMBER: 144:7075
TITLE: Synthesis of doxorubicin-peptide conjugate with multidrug resistant tumor cell killing activity
AUTHOR(S): Liang, Jun F.; Yang, Victor C.
CORPORATE SOURCE: Department of Chemistry and Chemical Biology, Stevens Institute of Technology, Hoboken, NJ, 07030, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (2005), 15(22), 5071-5075
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 144:7075

AB Cell penetrating peptide TAT (CGGGYGRKKRRQRRR) was introduced into doxorubicin structure. Synthesized doxorubicin-peptide conjugate showed different intracellular distribution pattern and cell killing activity from those of free doxorubicin. Unlike free doxorubicin, doxorubicin-peptide conjugate was highly permeable to drug-resistant cells and was able to kill drug-resistant tumor cells efficiently.

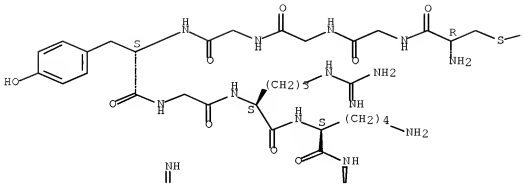
IT 869744-51-4P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of cell penetrating peptide-doxorubicin conjugate with multidrug resistant tumor cell killing activity)

RN 869744-51-4 HCAPLUS

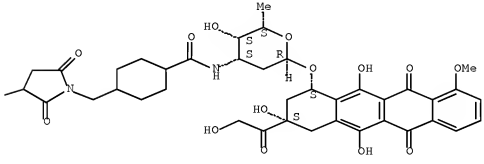
CN L-Arginine, L-cysteinylglycylglycylglycyl-L-tyrosylglycyl-L-arginyl-L-lysyl-L-lysyl-L-arginyl-L-arginyl-L-glutaminyl-L-arginyl-L-arginyl-, thioether with (8S,10S)-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[[[4-[(3-mercapto-2,5-dioxo-1-pyrrolidinyl)methyl]cyclohexyl]carbonyl]amino]-α-L-lyxo-hexopyranosyl]oxy]-5,12-naphthacenedione (9CI) (CA INDEX NAME)

Absolute stereochemistry.

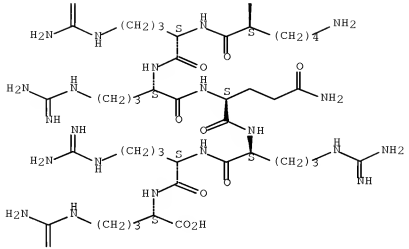
PAGE 1-A



PAGE 1-B



PAGE 2-A



PAGE 3-A

REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

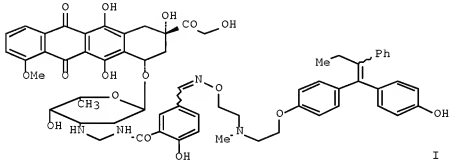
L29 ANSWER 6 OF 10 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:346801 HCAPLUS Full-text
DOCUMENT NUMBER: 142:411587
TITLE: Targeted drug-formaldehyde conjugates and methods of making and using the same
INVENTOR(S): Koch, Tad H.; Coleman, Michael P.; Cogan, Peter S.; Burke, Patrick J.; Post, Glen C.; Burkhart, David J.; McKenzie, Andrew R.; Jackson, Katrina L.; Kalet, Brian T.
PATENT ASSIGNEE(S): The Regents of the University of Colorado, USA
SOURCE: PCT Int. Appl., 180 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005034856	A2	20050421	WO 2004-US29095	20040907
WO 2005034856	A3	20050811		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 20070275911 A1 20071129 US 2007-570471 20070423
PRIORITY APPLN. INFO.: US 2003-500608P P 20030905
WO 2004-US29095 W 20040907
OTHER SOURCE(S): CASREACT 142:411587; MARPAT 142:411587
GI



I

AB This invention disclosed a prodrug platform technol. for improving the therapeutic value of a variety of parent drug compds. by altering and improving drug characteristics such as aqueous solubility, hydrolytic stability, therapeutic index, toxicity profile, pharmacokinetics and selectivity while allowing the potential for synthetic elaboration. The prodrug platform of the general form D-X-T (D = therapeutic drug moiety; X = linking moiety; T = biol. activity targeting moiety) is particularly well suited for targeting therapeutic drugs, including anti-tumor drugs and antibiotics, to specific receptors on target cells (e.g., cancer cells and bacteria). The platform is a technol. for providing an improved, pre-activated form of a therapeutic drug, and for optionally targeting such drug to target cells or biol. mols. Thus, the oxime prodrug I was prepared and consists of a doxorubicin antitumor moiety tethered via a salicylamide moiety to a 4-hydroxytamoxifen estrogen receptor binding moiety. The invention is broadly applicable to many different therapeutic drugs, as well as to a variety of diseases and conditions, including a variety of forms of cancer and bacterial infections.

IT 850256-45-0P 850256-63-2P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of targeted drug-formaldehyde conjugates for therapeutic use as
anticancer and antibiotic prodrugs)

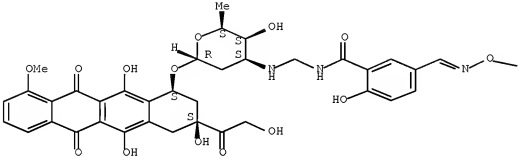
RN 850256-45-0 HCAPLUS

CN 5,12-Naphthacenedione, 10-[[3-[[[[5-[[1-[(L-cysteinyl-L-α-aspartyl-L-cysteinyl-L-arginylglycyl-L-α-aspartyl-L-cysteinyl-L-phenylalanyl-L-cysteinyl)amino]-5-oxo-3,9-dioxa-2,6-diazaundec-1-en-1-yl]-2-

hydroxybenzoyl]amino]methyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

PAGE 1-A



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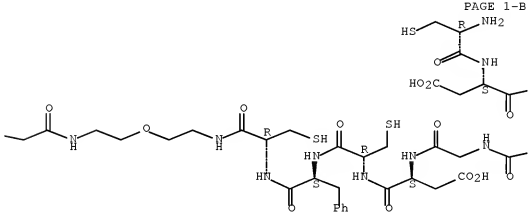

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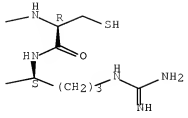
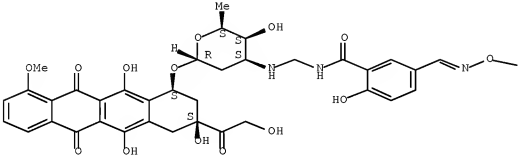


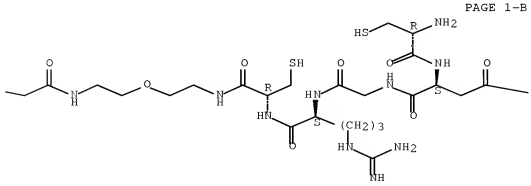
RN 850256-63-2 HCAPLUS
CN 5,12-Naphthacenedione, 10-[[3-[[[5-[11-[(L-cysteinyl-L-asparaginylglycyl-L-arginyl-L-cysteinyl)amino]-5-oxo-3,9-dioxa-2,6-diazaundec-1-en-1-yl]-2-hydroxybenzoyl]amino]methyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

PAGE 1-A



PAGE 1-B



—NH2

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 7 OF 10 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:6106 HCAPLUS Full-text
DOCUMENT NUMBER: 143:286663
TITLE: Doxorubicin-formaldehyde conjugates targeting αvβ3 integrin
AUTHOR(S): Burkhart, David J.; Kalet, Brian T.; Coleman, Michael P.; Post, Glen C.; Koch, Tad H.
CORPORATE SOURCE: Department of Chemistry and Biochemistry, University of Colorado, Boulder, CO, USA
SOURCE: Molecular Cancer Therapeutics (2004), 3(12), 1593-1604
CODEN: MCTOCF; ISSN: 1535-7163
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 143:286663

AB We have reported the synthesis and biol. evaluation of a prodrug to a doxorubicin active metabolite. Under physiol. conditions, release of the active metabolite, a conjugate of doxorubicin with formaldehyde, occurs with a half-life of 1 h. To direct this prodrug to tumor, we designed two conjugates of the prodrug, doxsaliform, with the αvβ3-targeting peptides, CDCRGDCFC (RGD-4C) and cyclo(N-Me-VRGDf) (Cilengitide). We now report the synthesis of these doxsaliform-peptide conjugates and their evaluation using MDA-MB-435 cancer cells. A hydroxylamine ether tether was used to attach 5"-formyldoxsaliform to RGD-4C in its acyclic form via an oxime functional group. The construct acyclic-RGD-4C-doxsaliform showed good binding affinity for αvβ3 in the vitronectin cell adhesion assay (IC50 = 10 nmol/L) and good growth inhibition of MDA-MB-435 breast cancer cells (IC50 = 50 nmol/L). In its bicyclic forms, RGD-4C showed less affinity for αvβ3 and significantly less water solubility Cyclo(N-Me-VRGDf) was modified by substitution of D-4-aminophenylalanine for D-phenylalanine to provide a novel attachment point for doxsaliform. The conjugate, cyclo(N-Me-VRGDf-NH)-doxsaliform, maintained a high affinity for αvβ3 (IC50 = 5 nmol/L) in the vitronectin cell adhesion assay relative to the peptide bearing only the tether (0.5 nmol/L). The IC50 for growth inhibition of MDA-MB-435 cells was 90 nmol/L. Flow cytometry and growth inhibition expts. suggest that the complete drug construct does not penetrate through the plasma membrane, but the active metabolite does on release from the targeting group. These drug conjugates could have significantly reduced side effects and are promising candidates for in vivo evaluation in tumor-bearing mice.

IT 863985-30-2P

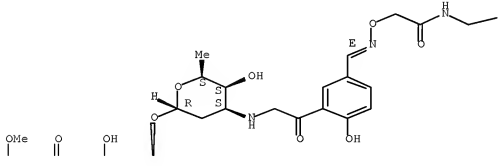
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and antitumor activity of doxorubicin-formaldehyde peptide conjugates targeting αvβ3 integrin)

RN 863985-30-2 HCAPLUS

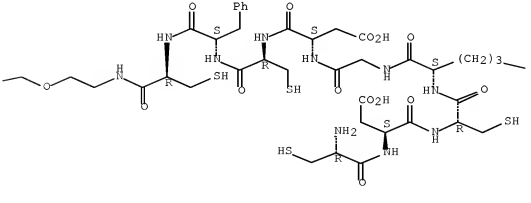
CN 5,12-Naphthacenedione, 10-[[3-[[2-[5-[(1E)-11-[(L-cysteinyl-L-α-aspartyl-L-cysteinyl-L-arginylglycyl-L-α-aspartyl-L-cysteinyl-L-phenylalanyl-L-cysteinyl)amino]-5-oxo-3,9-dioxa-2,6-diazaundec-1-en-1-yl]-2-hydroxyphenyl]-2-oxoethyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A

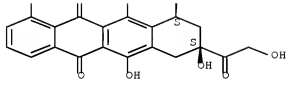


PAGE 1-B



PAGE 1-C

PAGE 2-A



REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 8 OF 10 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2004:610128 HCAPLUS Full-text
DOCUMENT NUMBER: 141:157478
TITLE: Peptides which target tumor and endothelial cells, compositions and uses thereof
INVENTOR(S): Allan, Amy L.; Yoon, Won Hyung; Gladstone, Patricia L.; Ternansky, Robert J.; Parry, Graham; Donate, Fernando; Mazar, Andrew
PATENT ASSIGNEE(S): Attenuon, Llc, USA
SOURCE: PCT Int. Appl., 117 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004063213	A2	20040729	WO 2003-US37895	20031125
WO 2004063213	A3	20050303		
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RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2506813	A1	20040729	CA 2003-2506813	20031125

AU	2003298726	A1	20040810	AU 2003-298726	20031125
US	20040162239	A1	20040819	US 2003-723144	20031125
US	20050020810	A1	20050127	US 2003-722843	20031125
EP	1569678	A2	20050907	EP 2003-796483	20031125
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CN	1741808	A	20060301	CN 2003-80109204	20031125
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JP	2006515866	T	20060608	JP 2005-512876	20031125
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MX	2005005545	A	20051018	MX 2005-5545	20050525
NO	2005003112	A	20050805	NO 2005-3112	20050624
IN	2005KN01228	A	20070126	IN 2005-KN1228	20050624
PRIORITY APPLN. INFO.:				US 2002-429174P P	20021125
				US 2003-475539P P	20030602
				WO 2003-US37895 W	20031125

OTHER SOURCE(S): MARPAT 141:157478

AB The invention relates generally to peptide analogs of Ac-PHSCN-NH2 which target tumor and endothelial cells and have antitumor, antiangiogenic and antimetastatic activity and to methods for their synthesis and use in pharmaceutical compns. for treating, preventing and detecting diseases characterized by tumor growth, metastasis and angiogenesis. The peptide analogs may serve, inter alia, as carriers of radioactivity, PET-active compds., toxins, fluorescent mols. and PEG mols. Peptides R1[(NHCHR2CO)0-1(X1)0-100]m-X2-X3-X4-X5-X6-[(X7)0-1(NHCHR3CO)0-1]nNR4R5 [R1 is (un)substituted acyl, alkyl, cycloalkyl or imino, or acyl chelate; R2 is substituted alkyl; R4, R5 are (un)substituted alkyl; X1, X7 are NH(CH:CH)1-6CO, NH(CH2)1-6CO, NHCHMeCO; X2-X6 are α-amino acids which are defined; m, n are 0 or 1, with the proviso that R1 is not acetyl when R4 and R5 are H and m and n are 0] are claimed. Thus, Ac-Pro-His-Ser-Cys(Ac)-Asn-OH was prepared by the solid-phase method and coupled to doxorubicin hydrochloride to afford the conjugate.

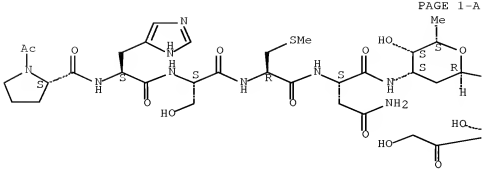
IT 729594-71-2P 729594-72-3P 729594-73-4P
RL: DGN (Diagnostic use); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of peptides which target tumor and endothelial cells)

RN 729594-71-2 HCAPLUS

CN 5,12-Naphthacenedione, 10-[[3-[(1-acetyl-L-prolyl-L-histidyl-L-seryl-S-methyl-L-cysteinyl-L-asparaginyl)amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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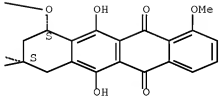

RN 729594-72-3 HCAPLUS
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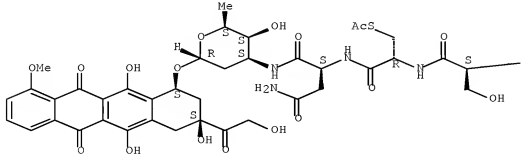
Absolute stereochemistry.

PAGE 1-A



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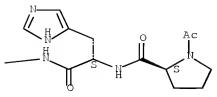
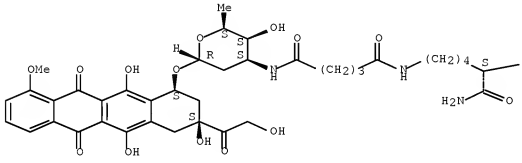


RN 729594-73-4 HCAPLUS

CN L-Lysinamide, 1-acetyl-L-prolyl-L-histidyl-L-seryl-S-methyl-L-cysteinyl-L-asparaginylglycylglycyl-N6-(4-carboxy-1-oxobutyl)-, amide with (8S,10S)-10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-5,12-naphthacenedione (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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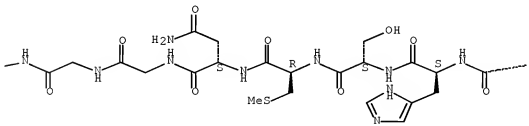


REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 9 OF 10 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2000:911119 HCAPLUS Full-text
DOCUMENT NUMBER: 134:66133
TITLE: Chemotherapeutic agent-peptide compositions for treating chemotherapy-resistant tumor cells, and targeted chemotherapy compositions
INVENTOR(S): Tuszynski, George; Williams, Taffy; Actor, Paul
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000078359	A2	20001228	WO 2000-US16955	20000621
WO 2000078359	A3	20020124		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-140310P P 19990621

AB The invention provides methods and compns. for treating cancer and chemotherapy-resistant cancers comprising a chemotherapeutic agent conjugated to or co-administered with a peptide.

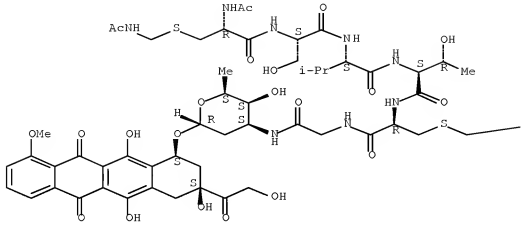
IT 313950-23-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(chemotherapeutic agent-peptide compns. for treating chemotherapy-resistant tumor cells, and targeted chemotherapy compns.)

RN 313950-23-1 HCAPLUS

CN 5,12-Naphthacenedione, 10-[[3-[[N-acetyl-S-[(acetylamino)methyl]-L-cysteinyl-L-seryl-L-valyl-L-threonyl-S-[(acetylamino)methyl]-L-cysteinylglycyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

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REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 10 OF 10 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1992:241931 HCAPLUS Full-text
DOCUMENT NUMBER: 116:241931
ORIGINAL REFERENCE NO.: 116:40889a,40892a
TITLE: Cell-internalizable conjugates and complexes including intracellularly-cleavable moieties
INVENTOR(S): Clark, Brian R.; Deshpande, Shrikant; Nag, Bishwajit
PATENT ASSIGNEE(S): Biospan Corp., USA
SOURCE: PCT Int. Appl., 68 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9118012	A1	19911128	WO 1991-US3352	19910514
W: CA, JP, US				

RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE
US 5169934 A 19921208 US 1990-523334 19900514
CA 2059649 A1 19911115 CA 1991-2059649 19910514
EP 482185 A1 19920429 EP 1991-910733 19910514
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE
JP 05502886 T 19930520 JP 1991-510427 19910514
US 5334391 A 19940802 US 1992-890187 19920529
PRIORITY APPLN. INFO.: US 1990-523334 A2 19900514
WO 1991-US3352 W 19910514

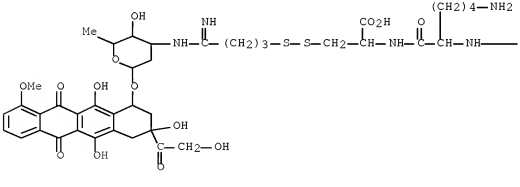
AB A cell-internalizable, intracellularly-cleavable conjugate comprises E-Z-Q [E = effector moiety, e.g., receptor (ant)agonist, growth factor, antineoplastic agent, oligonucleotide, antibody, antifungal agent, enzyme inhibitor, protein inhibitor, etc.; Z = intracellularly cleavable linkage; Q = organic moiety, e.g. oligonucleotide, antisense mol., ribozyme, peptide recognized by other organic moiety (e.g. major histocompatibility complex mol. (MHC)), etc.]. The conjugate may be complexed with an organic moiety facilitating delivery of the conjugate to and internalization of the conjugate by a target cell, e.g. a ligand for a cell surface receptor, a growth factor, a cytokine, etc. The conjugates are useful for therapy or diagnosis. Adriamycin was reacted with 2-iminothiolane and 2,2-dithiodipyridine and then with AcNH-Ala-Ser-Gln-Ala-Arg-Pro-Ser-Gln-Arg-His-Gly-Ser-Lys-Cys [Ac-myelin basic protein (AcMBP) peptide analog] to form a disulfide-linked peptide-adriamycin derivative (I). MBP-specific T-cell clone AJ1.2 was depleted by .apprx.85% by I complexed with I-Ak MHC antigen at a dose in humans equivalent to .apprx.120mg of the complex.

IT 141496-99-3P 141497-01-0P
RL: PREP (Preparation)
(preparation of and cell targeting with)

RN 141496-99-3 HCAPLUS

CN L-Alanine, N-acetyl-L-alanyl-L-seryl-L-glutaminyl-L-alanyl-L-arginyl-L-prolyl-L-glutaminyl-L-arginyl-L-histidylglycyl-L-seryl-L-lysyl-3-[[4-imino-4-[[2,3,6-trideoxy-1-O-[1,2,3,4,6,11-hexahydro-3,5,12-trihydroxy-3-(hydroxyacetyl)-10-methoxy-6,11-dioxo-1-naphthacenyl]-α-L-lyxo-hexopyranos-3-yl]amino]butyl]dithio]-, (1R-cis)- (9CI) (CA INDEX NAME)

PAGE 1-A



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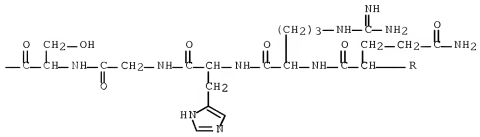

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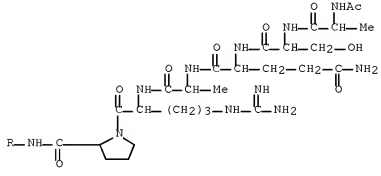
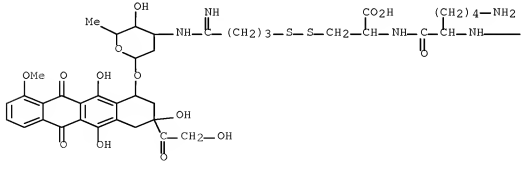


RN 141497-01-0 HCAPLUS

CN L-Alanine, N-acetyl-L-alanyl-L-seryl-L-glutaminyl-L-alanyl-L-arginyl-L-prolyl-L-seryl-L-glutaminyl-L-arginyl-L-histidylglycyl-L-seryl-L-lysyl-3-[[4-imino-4-[[2,3,6-trideoxy-1-O-[1,2,3,4,6,11-hexahydro-3,5,12-trihydroxy-3-(hydroxyacetyl)-10-methoxy-6,11-dioxo-1-naphthacenyl]-α-L-lyxo-hexopyranos-3-yl]amino]butyl]dithio]-, (1R-cis)- (9CI) (CA INDEX NAME)

PAGE 1-A



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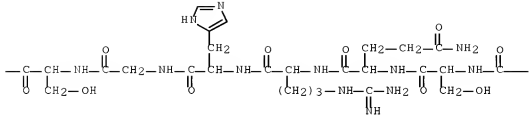

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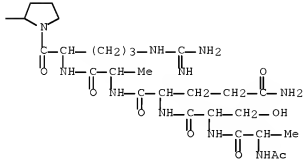

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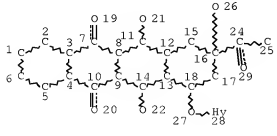

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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
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NUMBER OF NODES IS 28

STEREO ATTRIBUTES: NONE
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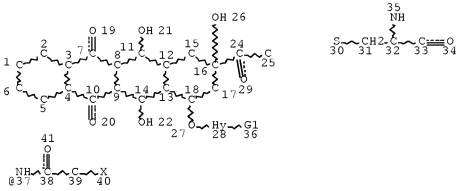

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DEFAULT ECLEVEL IS LIMITED

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NUMBER OF NODES IS 40

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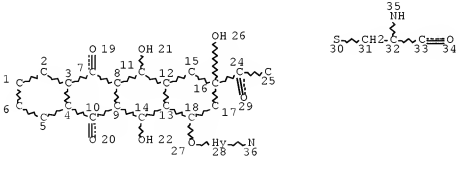

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=> d ibib abs hitstr l36 1-20

L36  ANSWER 1 OF 20  HCAPLUS  COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER:         2008:1210491  HCAPLUS  Full-text
DOCUMENT NUMBER:          149:448733
TITLE:                    Preparation of peptide prodrugs modified with a
                          1,2,3,4-cyclobutanetetracarboxylic acid derived moiety
                          useful in treatment and diagnosis of tumors and
                          inflammatory diseases
INVENTOR(S):              Matthieu, Michel; Dubois, Vincent; Tranchant,
                          Isabelle; Kearsey, Jonathan
PATENT ASSIGNEE(S):       Diatos, Fr.
SOURCE:                   PCT Int. Appl., 96pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   2
PATENT INFORMATION:

     PATENT NO.          KIND   DATE        APPLICATION NO.         DATE
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     WO 2008120098        A2    20081009    WO 2008-IB808           20080403
     WO 2008120098        A3    20090108
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             CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES,
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PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM,
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
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AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA
EP 1977765 A1 20081008 EP 2007-300920 20070403
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AL, BA, HR, MK, RS
PRIORITY APPLN. INFO.: EP 2007-300920 A 20070403
US 2007-989486P P 20071121
OTHER SOURCE(S): MARPAT 149:448733
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention is related to the preparation of peptide prodrugs I [L1, L2 = independently a covalent bond or a linking moiety, the linking moiety should include at least two organic functional groups, one organic functional group that can bind to the 1,2,3,4-cyclobutanetetracarboxylic acid and a second organic functional group that allows binding to the oligopeptide moiety (L1) or one functional group that can bind to the oligopeptide moiety and a second organic functional group that allows binding to D (L2); X = (CH2)n; X' = (CH2)m; X'' = (CH2)p; X''' = (CH2)q; n, m, p, q = independently 0-10; Y = cleavable oligopeptide moiety by at least one specific and/or selective peptidase that is present in the extracellular environment of target cells; D = therapeutic agent or marker] which improve the therapeutic index and the solubility of the therapeutic agent and are intended for the treatment and/or diagnosis of tumors and/or inflammatory reactions. Thus, tetraAcid-ALAL-doxorubicin II was prepared and showed stability in human plasma after 2 h incubation. II was evaluated for its in vivo efficacy in the LS 174T tumor model and in vitro reactivation into metabolites (leucyl-doxorubicin and doxorubicin) by tumor homogenates. A coumarin analog III was prepared for use as a marker for diagnosis purposes (no data).

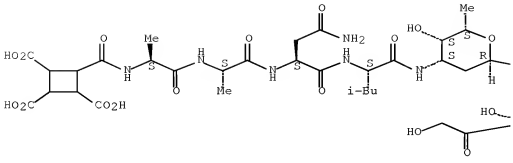
IT 1068660-47-8P 1068660-48-9P 1068660-50-3P
1068660-51-4P
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; peptide prodrugs useful in treatment and diagnosis of tumors and inflammatory diseases)

RN 1068660-47-8 HCAPLUS

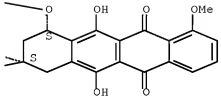
CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[[N-[(2,3,4-tricarboxycyclobutyl)carbonyl]-L-alanyl-L-alanyl-L-asparaginyl-L-leucyl]amino]-α-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



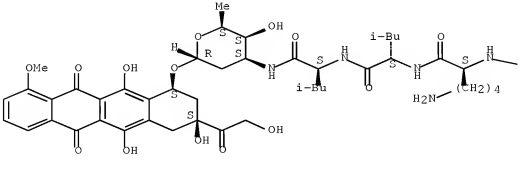
PAGE 1-B



RN 1068660-48-9 HCAPLUS
CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[[N-[(2,3,4-tricarboxycyclobutyl)carbonyl]-L-alanyl-L-leucyl-L-lysyl-L-leucyl-L-leucyl]amino]-α-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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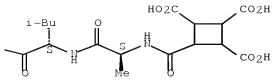
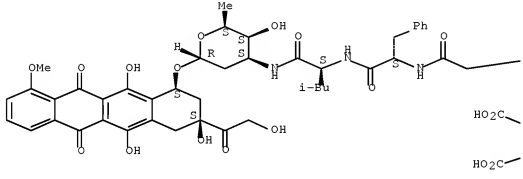


RN 1068660-50-3 HCAPLUS
CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[[N-[(2,3,4-tricarboxycyclobutyl)carbonyl]-L-alanyl-L-tyrosylglycylglycyl-L-phenylalanyl-L-leucyl]amino]-α-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)-
(CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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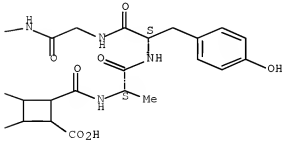
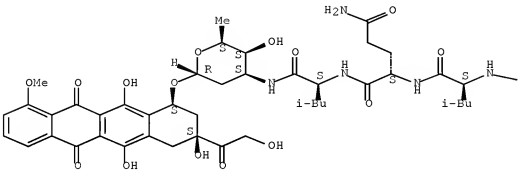


RN 1068660-51-4 HCAPLUS
CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[[N-[(2,3,4-

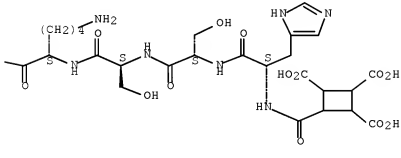
tricarboxycyclobutyl)carbonyl]-L-histidyl-L-seryl-L-seryl-L-lysyl-L-leucyl-L-glutaminyl-L-leucyl]amino]-α-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)-
(CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

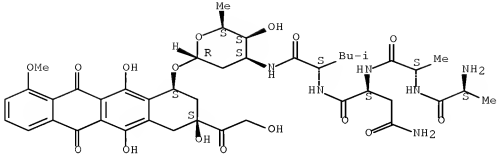


PAGE 1-B



IT 1068554-19-7P 1068554-20-0P 1068554-21-1P
1068554-23-3P 1068660-49-0P 1068660-52-5P
RL: PRPH (Prophetic); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; peptide prodrugs useful in treatment and diagnosis of tumors and inflammatory diseases)
RN 1068554-19-7 HCAPLUS
CN INDEX NAME NOT YET ASSIGNED

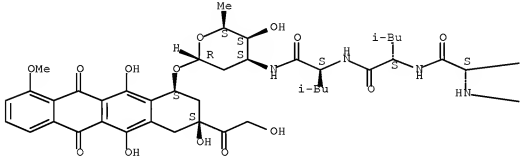
Absolute stereochemistry.



RN 1068554-20-0 HCAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.

PAGE 1-A



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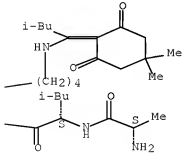
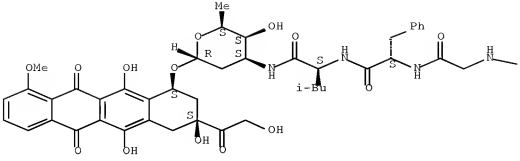


RN 1068554-21-1 HCAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.

PAGE 1-A



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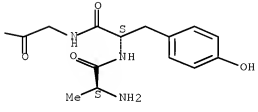
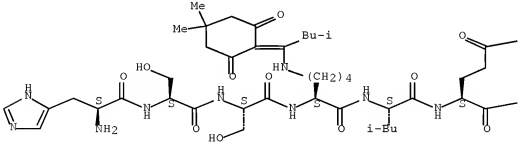


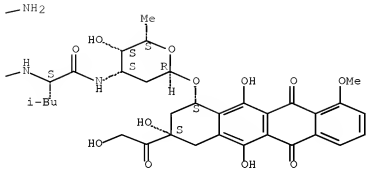
RN 1068554-23-3 HCAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.

PAGE 1-A



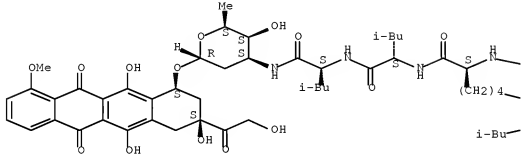
PAGE 1-B



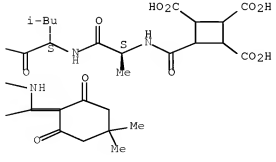
RN 1068660-49-0 HCAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.

PAGE 1-A



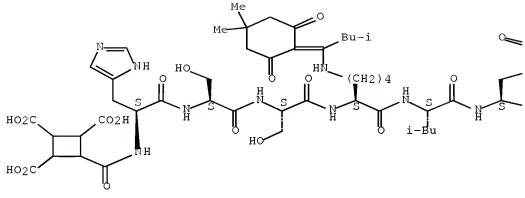
PAGE 1-B



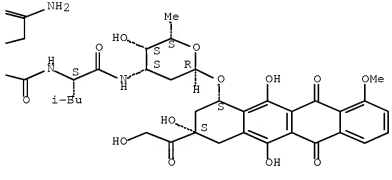
RN 1068660-52-5 HCAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.

PAGE 1-A



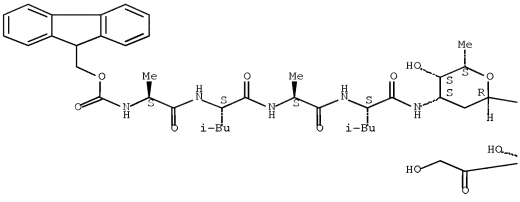
PAGE 1-B



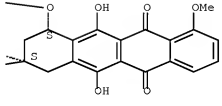
IT 1067286-73-0P
RL: PRPH (Prophetic); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of peptide prodrugs modified with a 1,2,3,4-cyclobutanetetracarboxylic acid derived moiety)
RN 1067286-73-0 HCAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.

PAGE 1-A

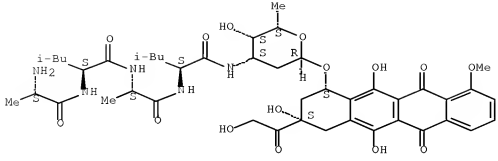


PAGE 1-B



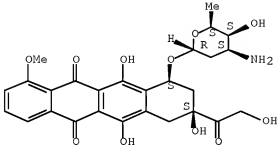
IT 757916-96-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of peptide prodrugs modified with a 1,2,3,4-cyclobutanetetracarboxylic acid derived moiety)
RN 757916-96-4 HCAPLUS
CN 5,12-Naphthacenedione, 10-[[3-[(L-alanyl-L-leucyl-L-alanyl-L-leucyl)amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.



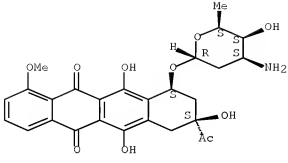
IT 23214-92-8, Doxorubicin
RL: PAC (Pharmacological activity); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(peptide prodrugs useful in treatment and diagnosis of tumors and inflammatory diseases)
RN 23214-92-8 HCAPLUS
CN 5,12-Naphthacenedione, 10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.



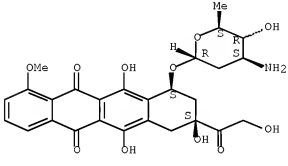
IT 20830-81-3, Daunorubicin 56420-45-2, Epirubicin 58957-92-9, Idarubicin 72496-41-4, THP-adriamycin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(peptide prodrugs useful in treatment and diagnosis of tumors and inflammatory diseases)
RN 20830-81-3 HCAPLUS
CN 5,12-Naphthacenedione, 8-acetyl-10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.



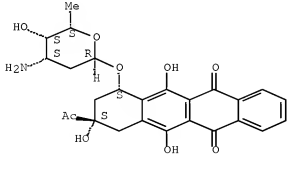
RN 56420-45-2 HCAPLUS
CN 5,12-Naphthacenedione, 10-[(3-amino-2,3,6-trideoxy-α-L-arabino-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.



RN 58957-92-9 HCAPLUS
CN 5,12-Naphthacenedione, 9-acetyl-7-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-, (7S,9S)- (CA INDEX NAME)

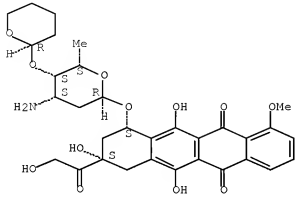
Absolute stereochemistry.



RN 72496-41-4 HCAPLUS
CN 5,12-Naphthacenedione, 10-[[3-amino-2,3,6-trideoxy-4-O-[(2R)-tetrahydro-2H-pyran-2-yl]-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-

trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.



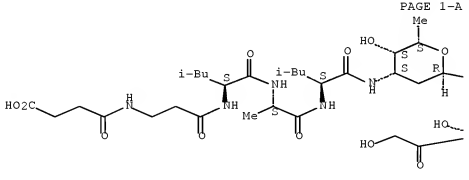
IT 274912-87-7P 1067286-48-9P 1067643-48-4P
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); PKT (Pharmacokinetics); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of peptide prodrugs modified with a 1,2,3,4-cyclobutanetetracarboxylic acid derived moiety)

RN 274912-87-7 HCAPLUS

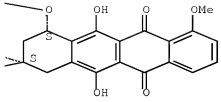
CN 5,12-Naphthacenedione, 10-[[3-[[N-(3-carboxy-1-oxopropyl)-β-alanyl-L-leucyl-L-alanyl-L-leucyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



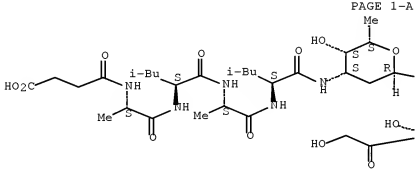
PAGE 1-B



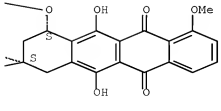
RN 1067286-48-9 HCAPLUS
CN 5,12-Naphthacenedione, 10-[[3-[[N-(3-carboxy-1-oxopropyl)-L-alanyl-L-leucyl-L-alanyl-L-leucyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

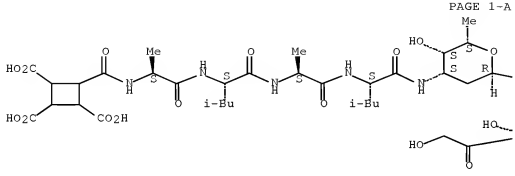


RN 1067643-48-4 HCAPLUS
CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[[N-[(2,3,4-

tricarboxycyclobutyl)carbonyl]-L-alanyl-L-leucyl-L-alanyl-L-leucyl]amino]-α-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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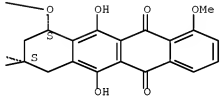


L36 ANSWER 2 OF 20 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2008:1205912 HCAPLUS Full-text
DOCUMENT NUMBER: 149:448732
TITLE: Preparation of peptide prodrugs modified with a 1,2,3,4-cyclobutanetetracarboxylic acid derived moiety useful in treatment and diagnosis of tumors and inflammatory diseases
INVENTOR(S): Matthieu, Michel; Dubois, Vincent; Tranchant, Isabelle; Kearsey, Jonathan
PATENT ASSIGNEE(S): Diatos, Fr.
SOURCE: Eur. Pat. Appl., 31pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1977765	A1	20081008	EP 2007-300920	20070403

R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, RS
WO 2008120098 A2 20081009 WO 2008-IB808 20080403
WO 2008120098 A3 20090108
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA
PRIORITY APPLN. INFO.: EP 2007-300920 A 20070403
US 2007-989486P P 20071121

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

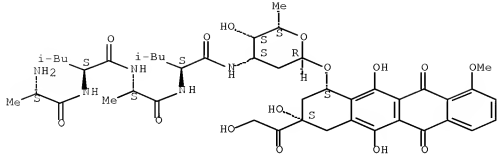
AB The invention is related to the preparation of peptide prodrugs I [L1, L2 = independently a covalent bond or a linking moiety; X = (CH2)n; X' = (CH2)m; X'' = (CH2)p; X''' = (CH2)q; n, m, p, q = independently 0-10; Y = cleavable oligopeptide moiety; D = therapeutic agent or marker] which improve the therapeutic index and the solubility of the therapeutic agent and are intended for the treatment and/or diagnosis of tumors and/or inflammatory reactions. Thus, tetraAcid-ALAL-doxorubicin II was prepared and showed stability in human plasma after 2 h incubation. II was evaluated for its in vivo efficacy in the LS 174T tumor model.

IT 757916-96-4P 1067286-73-0P
RL: PRPH (Prophetic); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of peptide prodrugs modified with a 1,2,3,4-cyclobutanetetracarboxylic acid derived moiety)

RN 757916-96-4 HCAPLUS

CN 5,12-Naphthacenedione, 10-[[3-[(L-alanyl-L-leucyl-L-alanyl-L-leucyl)amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, (8S,10S)- (CA INDEX NAME)

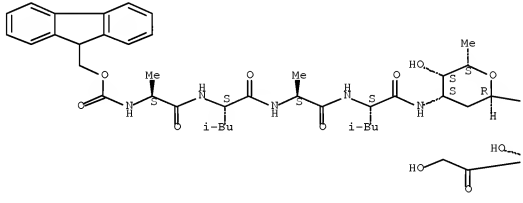
Absolute stereochemistry.



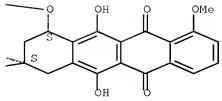
RN 1067286-73-0 HCAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



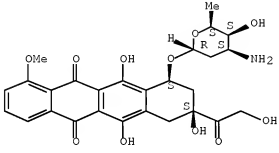
IT 23214-92-8, Doxorubicin

RL: PAC (Pharmacological activity); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(peptide prodrugs useful in treatment and diagnosis of tumors and inflammatory diseases)

RN 23214-92-8 HCAPLUS

CN 5,12-Naphthacenedione, 10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.

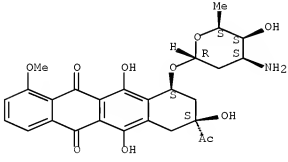


IT 20830-81-3, Daunorubicin 56420-45-2, Epirubicin 58957-92-9, Idarubicin 72496-41-4, THP-adriamycin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(peptide prodrugs useful in treatment and diagnosis of tumors and inflammatory diseases)

RN 20830-81-3 HCAPLUS

CN 5,12-Naphthacenedione, 8-acetyl-10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S,10S)- (CA INDEX NAME)

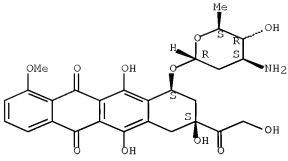
Absolute stereochemistry.



RN 56420-45-2 HCAPLUS

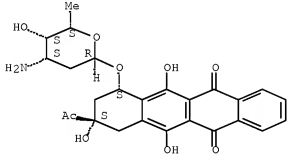
CN 5,12-Naphthacenedione, 10-[(3-amino-2,3,6-trideoxy-α-L-arabino-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.



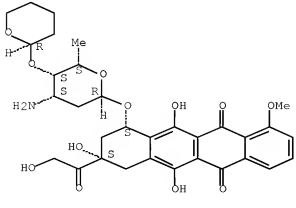
RN 58957-92-9 HCAPLUS
CN 5,12-Naphthacenedione, 9-acetyl-7-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-, (7S,9S)- (CA INDEX NAME)

Absolute stereochemistry.



RN 72496-41-4 HCAPLUS
CN 5,12-Naphthacenedione, 10-[[3-amino-2,3,6-trideoxy-4-O-[(2R)-tetrahydro-2H-pyran-2-yl]-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.



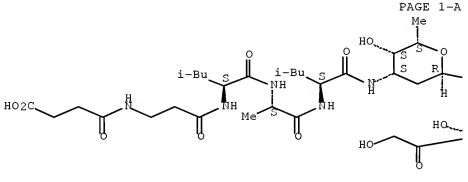
IT 274912-87-7P 1067286-48-9P 1067643-48-4P
RL: ADV (Adverse effect, including toxicity); PKT (Pharmacokinetics); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of peptide prodrugs modified with a 1,2,3,4-cyclobutanetetracarboxylic acid derived moiety)

RN 274912-87-7 HCAPLUS

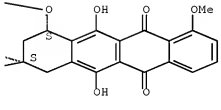
CN 5,12-Naphthacenedione, 10-[[3-[[N-(3-carboxy-1-oxopropyl)-β-alanyl-L-leucyl-L-alanyl-L-leucyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

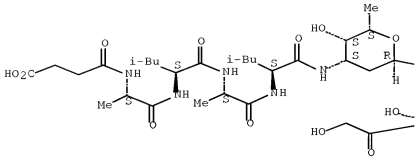


RN 1067286-48-9 HCAPLUS

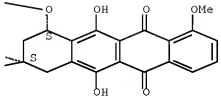
CN 5,12-Naphthacenedione, 10-[[3-[[N-(3-carboxy-1-oxopropyl)-L-alanyl-L-leucyl-L-alanyl-L-leucyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



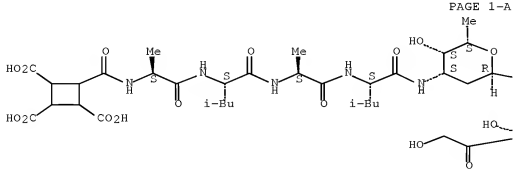
PAGE 1-B

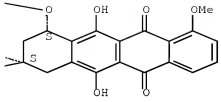


RN 1067643-48-4 HCAPLUS
CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[[N-[(2,3,4-tricarboxycyclobutyl)carbonyl]-L-alanyl-L-leucyl-L-alanyl-L-leucyl]amino]-α-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A





REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 3 OF 20 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2008:199454 HCAPLUS Full-text
DOCUMENT NUMBER: 149:323172
TITLE: Preclinical Toxicity, Toxicokinetics, and Antitumoral Efficacy Studies of DTS-201, a Tumor-Selective Peptidic Prodrug of Doxorubicin
AUTHOR(S): Ravel, Denis; Dubois, Vincent; Quinonero, Jerome; Meyer-Losic, Florence; Delord, JeanPierre; Rochaix, Philippe; Nicolazzi, Celine; Ribes, Fabien; Mazerolles, Catherine; Assouly, Elise; Vialatte, Karine; Hor, Ines; Kearsey, Jonathan; Trouet, Andre
CORPORATE SOURCE: Diatos S.A., Paris, Fr.
SOURCE: Clinical Cancer Research (2008), 14(4), 1258-1265
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB PURPOSE: There is a clear clin. need for cytotoxic drugs with a lower systemic toxicity. DTS-201 (CPI-0004Na) is a peptidic prodrug of doxorubicin that shows an improved therapeutic index in exptl. models. The purpose of the current study was to complete its preclin. characterization before initiation of phase I clin. trials. Exptl. Design: The preclin. development program consisted of a detailed assessment of the general and cardiac toxicity profiles of DTS-201 in mice, rats, and dogs, together with mass balance and antitumoral efficacy studies in rodents. Neprilysin and thimet oligopeptidase expression, two enzymic activators of DTS-201, was also characterized in human breast and prostate tumor biopsies. RESULTS: The target organs of DTS-201 toxicity in rodents and dogs are typically those of doxorubicin, albeit at much higher doses. Importantly, chronic treatment with DTS-201 proved to be significantly less cardiotoxic than with doxorubicin at doses up to 8-fold higher in rats. The mass balance study showed that [14C] DTS-201 does not accumulate in the body after i.v. administration. The improved therapeutic index of DTS-201 compared with free doxorubicin was confirmed in three tumor xenograft models of prostate, breast, and lung cancer. Neprilysin and/or thimet oligopeptidase are expressed in all exptl. human tumor types thus far tested as well as in a large majority of human breast and prostate tumor biopsies. CONCLUSION: DTS-201 gave promising results in terms of general toxicity, cardiovascular tolerance, and in vivo efficacy in xenograft mouse models compared with free doxorubicin. Taken together, these results and the

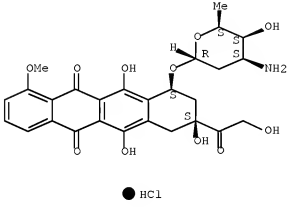
confirmation of the presence of activating enzymes in human tumor biopsies provide a strong rationale for a phase I clin. study in cancer patients.

IT 25316-40-9, Doxorubicin.hydrochloride 274912-87-7, DTS 201
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(DTS-201 did not accumulate in body after i.v. administration, showed less acute and cardiac toxicity than doxorubicin.HCl in rodent, dog while high antitumor efficacy in human prostate, breast, lung cancer xenografted mouse model)

RN 25316-40-9 HCAPLUS

CN 5,12-Naphthacenedione, 10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, hydrochloride (1:1), (8S,10S)- (CA INDEX NAME)

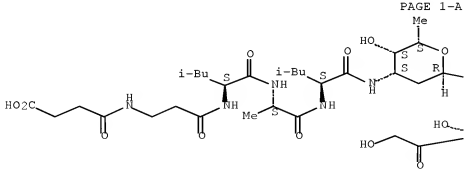
Absolute stereochemistry.

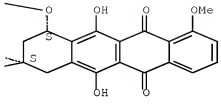


RN 274912-87-7 HCAPLUS

CN 5,12-Naphthacenedione, 10-[[3-[[N-(3-carboxy-1-oxopropyl)-β-alanyl-L-leucyl-L-alanyl-L-leucyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.





REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 4 OF 20 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2007:1064392 HCAPLUS Full-text
DOCUMENT NUMBER: 147:371832
TITLE: Anticancer drugs conjugated to antibody via an enzyme cleavable linker for treatment of neoplastic diseases
INVENTOR(S): Trouet, Andre; Dubois, Vincent
PATENT ASSIGNEE(S): Diatos, Fr.
SOURCE: PCT Int. Appl., 49pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007105027	A1	20070920	WO 2006-IB1185	20060310
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
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CA 2645347	A1	20070920	CA 2006-2645347	20060310
EP 1993608	A1	20081126	EP 2006-727587	20060310
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR				
PRIORITY APPLN. INFO.:			WO 2006-IB1185 W	20060310

AB This invention relates to the field of antibody-drug conjugates, and more particularly antibody-drug conjugates that are intended for the treatment and/or diagnosis of neoplastic diseases, such as tumors and/or inflammatory reactions in mammals including humans. Thus, reaction of doxorubicin-HCl (400

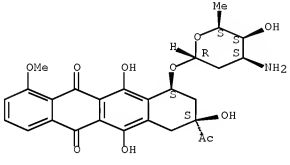
mg) with Fmoc-Ala-Leu-Ala-Leu-OH (500 mg) in presence of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) resulted in Ala-Leu-Ala-Leu-doxorubicin (578 mg). The non-internalizing antibody (50 mg/mL in H2O) was succinylated and the pH was adjusted to 7.5. The succinylated non-internalizing antibody (350 mg) was diluted to 2 mg/mL in 0.1 M sodium phosphate buffer, 0.5 M NaCl and 80 molar equivalents of Ala-Leu-Ala-Leu-doxorubicin diluted in 1 mL H2O were added, followed by 300 molar equivalents of ECDI as a coupling agent. The reaction took place at 4° for 24 h and under pH control to give a non-internalizing antibody-Ala-Leu-Ala-Leu-doxorubicin compound

IT 20830-81-3, Daunorubicin 23214-92-8, Doxorubicin 25316-40-9, Doxorubicin hydrochloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(anticancer drugs conjugated to antibody via enzyme cleavable oligopeptide linker for treatment of neoplastic and other diseases)

RN 20830-81-3 HCAPLUS

CN 5,12-Naphthacenedione, 8-acetyl-10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S,10S)- (CA INDEX NAME)

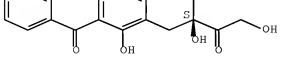
Absolute stereochemistry.



RN 23214-92-8 HCAPLUS

CN 5,12-Naphthacenedione, 10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, (8S,10S)- (CA INDEX NAME)

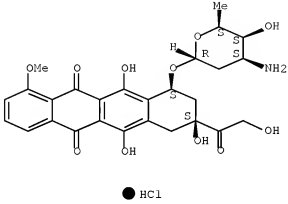
Absolute stereochemistry.



RN 25316-40-9 HCAPLUS

CN 5,12-Naphthacenedione, 10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, hydrochloride (1:1), (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.



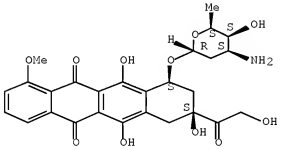
● HCl

IT 23214-92-8DP, Doxorubicin, conjugates with antibody and oligopeptide
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(anticancer drugs conjugated to antibody via enzyme cleavable oligopeptide linker for treatment of neoplastic and other diseases)

RN 23214-92-8 HCAPLUS

CN 5,12-Naphthacenedione, 10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 5 OF 20 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2006:1311805 HCAPLUS Full-text
DOCUMENT NUMBER: 146:68691
TITLE: Potentialization of the activation of high molecular weight prodrugs of doxorubicin

INVENTOR(S): Trouet, Andre; Dubois, Vincent
PATENT ASSIGNEE(S): Belg.
SOURCE: U.S. Pat. Appl. Publ., 34pp., Cont.-in-part of Appl. No. PCT/FR2004/002162.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20060281897	A1	20061214	US 2006-357966	20060222
FR 2858936	A1	20050225	FR 2003-10114	20030822
WO 2005021043	A2	20050310	WO 2004-FR2162	20040819
WO 2005021043	A3	20060615		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:		
FR 2003-10114	A	20030822
WO 2004-FR2162	A2	20040819
US 2005-665828P	P	20050329

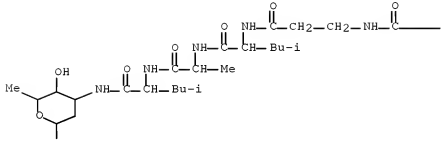
AB This invention is directed to a modified form of a prodrug of doxorubicin. A typical form of prodrug comprises a bulky group, a spacer, a structure that can be cleaved at or near the target cells and a therapeutic agent or a marker, whereby the spacer allows or facilitates the cleavage of the cleavable structure. The anti-tumor efficacy of PEG2000-(D-Ser)4-ala-leu-ala-leu-doxorubicin was determined in an HCT-116 human colon carcinoma xenograft model implanted s.c. in Swiss nude/nude mice. The compound was toxic at 300 and 400 μmol/ kg and induced a weight loss and the death of the animals. This toxicity suggests a more significant reactivation in the extra-blood compartment. The compound had a better anti-tumor efficacy than that of the control.

IT 916726-03-9P 916726-04-0P 916726-05-1P
916726-06-2P 916807-08-4P
RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(potentialization of activation of high mol. weight prodrugs of doxorubicin)

RN 916726-03-9 HCAPLUS

CN Poly(oxy-1,2-ethanediyl), α-methyl-ω-hydroxy-, 1''2-ether with (8S,10S)-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[[N-(3-hydroxy-1-oxopropyl)-D-seryl-D-seryl-D-seryl-D-seryl-β-alanyl-L-leucyl-L-alanyl-L-leucyl]amino]-α-L-lyxo-hexopyranosyl]oxy]-5,12-naphthacenedione (CA INDEX NAME)

PAGE 1-A



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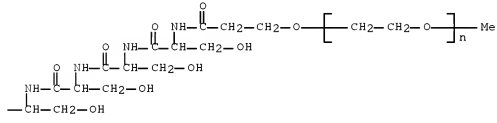

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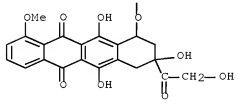
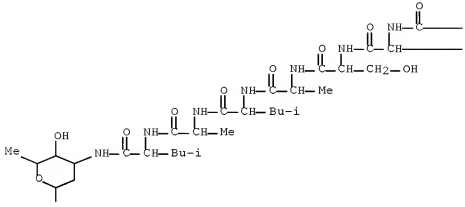


RN 916726-04-0 HCAPLUS

CN Poly(oxy-1,2-ethanediyl), α-methyl-ω-hydroxy-, 1''2-ether with (8S,10S)-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[[N-(3-hydroxy-1-oxopropyl)-D-seryl-D-seryl-D-seryl-D-seryl-L-alanyl-L-leucyl-L-alanyl-L-leucyl]amino]-α-L-lyxo-hexopyranosyl]oxy]-5,12-naphthacenedione (CA INDEX NAME)

PAGE 1-A



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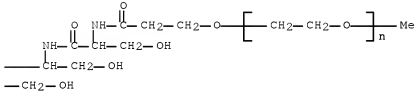

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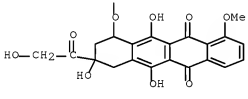
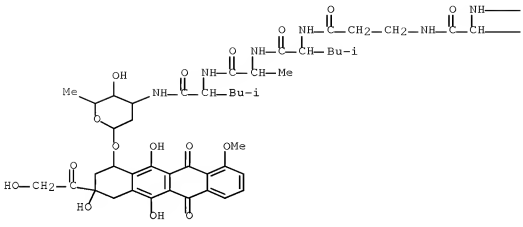


RN 916726-05-1 HCAPLUS

CN Poly(oxy-1,2-ethanediyl), α-methyl-ω-hydroxy-, 1''2-ether with (8S,10S)-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[[N-(3-hydroxy-1-oxopropyl)-D-seryl-β-alanyl-L-leucyl-L-alanyl-L-leucyl]amino]-α-L-lyxo-hexopyranosyl]oxy]-5,12-naphthacenedione (CA INDEX NAME)

PAGE 1-A



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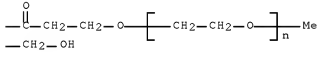
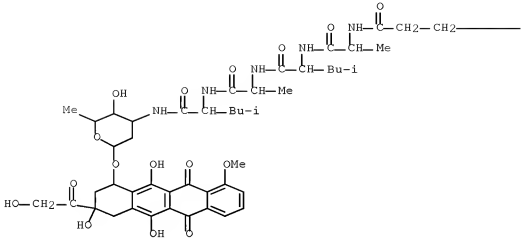


RN 916726-06-2 HCAPLUS

CN Poly(oxy-1,2-ethanediyl), α-methyl-ω-hydroxy-, 1''-ether with (8S,10S)-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[[N-(3-hydroxy-1-oxopropyl)-L-alanyl-L-leucyl-L-alanyl-L-leucyl]amino]-α-L-lyxo-hexopyranosyl]oxy]-5,12-naphthacenedione (CA INDEX NAME)

PAGE 1-A



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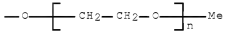
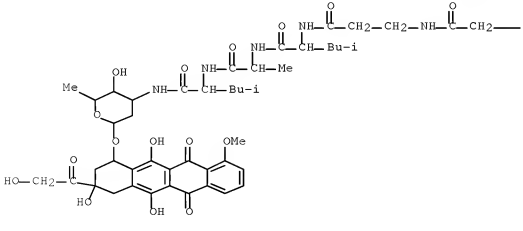


RN 916807-08-4 HCAPLUS

CN Poly(oxy-1,2-ethanediyl), α-methyl-ω-hydroxy-, 1''-ether with (8S,10S)-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[[N-(3-hydroxy-1-oxopropyl)-β-alanyl-L-leucyl-L-alanyl-L-leucyl]amino]-α-L-lyxo-hexopyranosyl]oxy]-5,12-naphthacenedione (CA INDEX NAME)

PAGE 1-A



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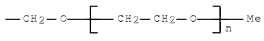
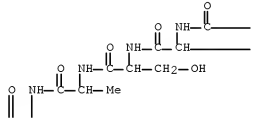


IT 916726-09-5P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(potentialization of activation of high mol. weight prodrugs of doxorubicin)

RN 916726-09-5 HCAPLUS

CN Poly(oxy-1,2-ethanediyl), α-methyl-ω-hydroxy-, 1''2-ether with (8S,10S)-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[[N-(3-hydroxy-1-oxopropyl)-D-seryl-D-seryl-D-seryl-D-seryl-D-seryl-D-seryl-D-seryl-D-seryl-L-alanyl-L-leucyl-L-alanyl-L-leucyl]amino]-α-L-lyxo-hexopyranosyl]oxy]-5,12-naphthacenedione (CA INDEX NAME)

PAGE 1-A



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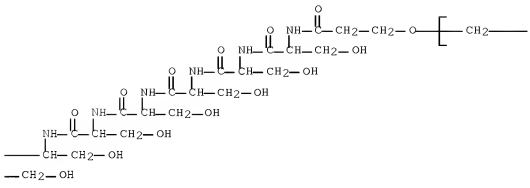

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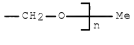

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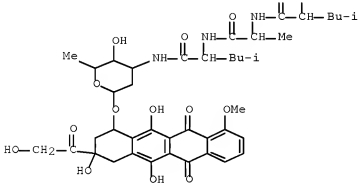
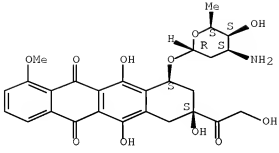


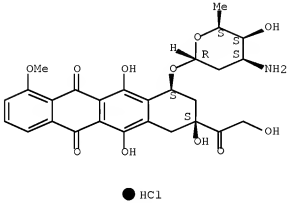
IT 23214-92-8, Doxorubicin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(potentialization of activation of high mol. weight prodrugs of doxorubicin)
RN 23214-92-8 HCAPLUS
CN 5,12-Naphthacenedione, 10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.



IT 25316-40-9, Doxorubicin hydrochloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(potentialization of activation of high mol. weight prodrugs of doxorubicin)
RN 25316-40-9 HCAPLUS
CN 5,12-Naphthacenedione, 10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, hydrochloride (1:1), (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.



● HCl

L36 ANSWER 6 OF 20 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2006:1170606 HCAPLUS Full-text
DOCUMENT NUMBER: 146:176401
TITLE: Thimet oligopeptidase (EC 3.4.24.15) activates CPI-0004Na, an extracellularly tumour-activated prodrug of doxorubicin
AUTHOR(S): Dubois, V.; Nieder, M.; Collot, F.; Negrouk, A.; Nguyen, T. T.; Gangwar, S.; Reitz, B.; Wattiez, R.; Dasnois, L.; Trouet, A.
CORPORATE SOURCE: Laboratory of Cell Biology, Universite Catholique de Louvain, Louvain-La-Neuve, 1348, Belg.
SOURCE: European Journal of Cancer (2006), 42(17), 3049-3056
CODEN: EJCAEL; ISSN: 0959-8049
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

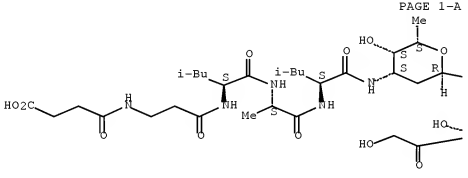
AB CPI-0004Na is a tetrapeptidic extracellularly tumor-activated prodrug of doxorubicin. The tetrapeptide structure ensures blood stability and selective cleavage by unidentified peptidase(s) released by tumor cells. The purpose of this work was to identify the enzyme responsible for the first rate-limiting step of CPI-0004Na activation, initially attributed to a 70 kDa acidic (pI = 5.2) metallopeptidase active at neutral pH that was subsequently purified from HeLa cell homogenates. Two electrophoretic bands were isolated and identified by matrix-assisted laser desorption ionization-time of flight (MALDI-tof) and electrospray ionization-quadrupole-time of flight (ESI-Q-tof) mass spectrometry as thimet oligopeptidase (TOP). The identity of the CPI-0004Na activating enzyme and TOP was further supported by the similar substrate specificity of the purified enzyme and recombinant TOP, by thiol stimulation of CPI-0004Na cleavage by cancer cell conditioned media (unique characteristic of TOP) and by the inhibition of CPI-0004Na activation by specific inhibitors or immunopptn. Although other enzymes can be involved, TOP clearly appears to be a likely candidate for extracellular activation of the CPI-0004Na prodrug.

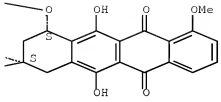
IT 274912-87-7, CPI 0004Na
RL: PAC (Pharmacological activity); BIOL (Biological study)
(thimet oligopeptidase was responsible for first rate-limiting step of CPI-0004Na activation in human cervical adenocarcinoma cell)

RN 274912-87-7 HCAPLUS

CN 5,12-Naphthacenedione, 10-[[3-[[N-(3-carboxy-1-oxopropyl)-β-alanyl-L-leucyl-L-alanyl-L-leucyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, (8S,10S)- (CA INDEX NAME)

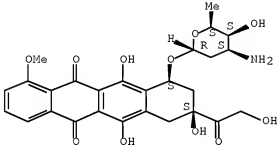
Absolute stereochemistry.





IT 23214-92-8, Doxorubicin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(thimet oligopeptidase was responsible for first rate-limiting step of doxorubicin prodrug CPI-0004Na activation in human cervical adenocarcinoma cell)
RN 23214-92-8 HCAPLUS
CN 5,12-Naphthacenedione, 10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 7 OF 20 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:159927 HCAPLUS Full-text
DOCUMENT NUMBER: 142:254652
TITLE: Potentiation of the activation of high-molecular-weight prodrugs for therapeutic or diagnostic use
INVENTOR(S): Trouet, Andre; Dubois, Vincent
PATENT ASSIGNEE(S): Diatos, Fr.
SOURCE: Fr. Demande, 64 pp.
CODEN: FRXXBL
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 2858936	A1	20050225	FR 2003-10114	20030822
AU 2004268405	A1	20050310	AU 2004-268405	20040819
CA 2536442	A1	20050310	CA 2004-2536442	20040819
WO 2005021043	A2	20050310	WO 2004-FR2162	20040819
WO 2005021043	A3	20060615		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1701743	A2	20060920	EP 2004-786328	20040819
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				
BR 2004013843	A	20061024	BR 2004-13843	20040819
JP 2007503382	T	20070222	JP 2006-523656	20040819
US 20060281897	A1	20061214	US 2006-357966	20060222
PRIORITY APPLN. INFO.:			FR 2003-10114 A	20030822
			WO 2004-FR2162 W	20040819
			US 2005-665828P P	20050329

AB The invention discloses a modified form of a prodrug. The prodrugs of the invention include a bulky group, a spacer, a structure cleavable in the circulation, and a therapeutic agent or a marker. The spacer allows or facilitates the cleavage of the cleavable structure. Preparation of PEG-peptide-doxorubicin conjugates is included.

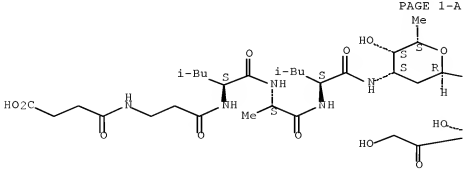
IT 274912-87-7

RL: PAC (Pharmacological activity); BIOL (Biological study) (potentiation of activation of high-mol.-weight prodrugs for therapeutic or diagnostic use)

RN 274912-87-7 HCAPLUS

CN 5,12-Naphthacenedione, 10-[[3-[[N-(3-carboxy-1-oxopropyl)-β-alanyl-L-leucyl-L-alanyl-L-leucyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.



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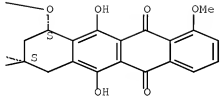
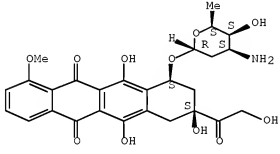


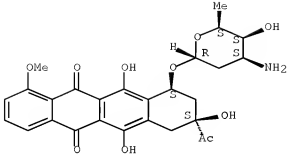
IT 23214-92-8, Doxorubicin
RL: PAC (Pharmacological activity); RCT (Reactant); BIOL (Biological study); RACT (Reactant or reagent)
(potentiation of activation of high-mol.-weight prodrugs for therapeutic or diagnostic use)
RN 23214-92-8 HCAPLUS
CN 5,12-Naphthacenedione, 10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.



IT 20830-81-3D, Daunorubicin, conjugates 23214-92-8D, Doxorubicin, conjugates
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(potentiation of activation of high-mol.-weight prodrugs for therapeutic or diagnostic use)
RN 20830-81-3 HCAPLUS
CN 5,12-Naphthacenedione, 8-acetyl-10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S,10S)- (CA INDEX NAME)

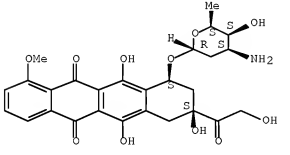
Absolute stereochemistry.



RN 23214-92-8 HCAPLUS

CN 5,12-Naphthacenedione, 10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 8 OF 20 HCAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2004:765541 HCAPLUS Full-text

DOCUMENT NUMBER: 142:106748

TITLE: CPI-0004Na, a new doxorubicin prodrug, reduces growth of 3LL-H61 carcinoma lung metastases in C57B1/6 mice

AUTHOR(S): Dasnols, Luc; Lebtahi, Karim; Abarca-Quinones, Jorge; Havaux, Nathalie; Dupont, Samuel; Dubois, Vincent; Trouet, Andre

CORPORATE SOURCE: Laboratory of Cell Biology & Institut des Sciences de la Vie, Universite catholique de Louvain, Louvain-La-Neuve, B-1348, Belg.

SOURCE: Journal of Experimental Therapeutics and Oncology (2004), 4(2), 167-169
CODEN: JETOFX; ISSN: 1359-4117

PUBLISHER: Old City Publishing

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The ETAP concept (Extracellularly Tumor-Activated Prodrug) is a new approach developed to overcome the lack of selectivity and the side effects responsible for the limited efficacy of chemotherapeutic agents. CPI-0004Na, a doxorubicin (Dox) prototype prodrug of this type, is less toxic than free Dox and showed

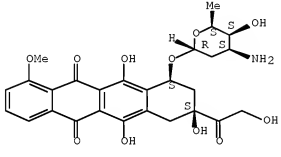
increased efficacy against s.c. human tumor xenografts. The aim of this study was to assess the efficacy of the prodrug vs Dox (given i.p.) at their maximal tolerated dose (MTD) for this administration schedule (129.3 μmol/kg and 12.93 μmol/kg, resp.) against exptl. induced 3LL-H61 carcinoma lung metastases in mice. Our results indicate that, Dox has no effect on the number of lung metastases while CPI-0004Na induces a 38.3% reduction on average When considering the effect on the proportion of the lungs' surface covered by metastases, Dox induces a 39% reduction while the prodrug CPI-0004Na is about two fold more active with a 71% decrease.

IT 23214-92-8, Doxorubicin
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(doxorubicin prodrug CPI-0004Na significantly reduced 3LL-H61 carcinoma cell lung metastases in mouse than doxorubicin suggesting its potent anti-tumor activity)

RN 23214-92-8 HCAPLUS

CN 5,12-Naphthacenedione, 10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.



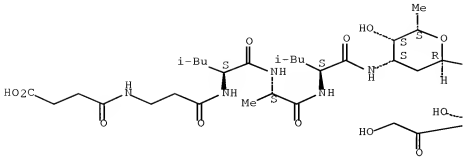
IT 274912-87-7, CPI 0004Na
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(doxorubicin prodrug CPI-0004Na significantly reduced 3LL-H61 carcinoma cell lung metastases in mouse than doxorubicin suggesting its potent anti-tumor activity)

RN 274912-87-7 HCAPLUS

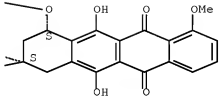
CN 5,12-Naphthacenedione, 10-[[3-[[N-(3-carboxy-1-oxopropyl)-β-alanyl-L-leucyl-L-alanyl-L-leucyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 9 OF 20 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2004:101021 HCAPLUS Full-text
DOCUMENT NUMBER: 140:146517
TITLE: Method for the synthesis of anthracycline-peptide conjugates
INVENTOR(S): Fernandez, Anne-Marie; Dubois, Vincent
PATENT ASSIGNEE(S): Universite Catholique de Louvain, Belg.; Diatos S.A.
SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004011033	A1	20040205	WO 2003-EP8082	20030723

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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2490495	A1	20040205	CA 2003-2490495		20030723
AU 2003250151	A1	20040216	AU 2003-250151		20030723
EP 1525002	A1	20050427	EP 2003-771079		20030723

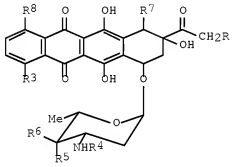
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

JP 2006504657	T	20060209	JP 2004-523773		20030723
US 20050239688	A1	20051027	US 2005-522565		20050620

PRIORITY APPLN. INFO.: EP 2002-447145 A 20020724
WO 2003-EP8082 W 20030723

OTHER SOURCE(S): CASREACT 140:146517; MARPAT 140:146517

GI



I

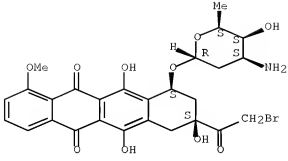
AB The invention relates to a method for the preparation of compds. I [R is -L-SCH2CH(NHR2)COR1, where L is an optional suitable linker arm, R1 is OH, NH2 or NH-peptide and R2 is H or -CO-peptide; R3 is OMe, OH or H; R4 is H or COCF3; R5 is OH, O-tetrahydropyranyl or H; R6, R7, R8 are OH or H] or their pharmaceutically-acceptable salts and intermediates which comprises halogenation of I [R is H, OH, O2CBu or O2CCH(OEt)2] and reaction of I (R = halo) at its 14-position with the thiol moiety of a peptide HSCH2CH(NHR2)COR1. Thus, daunorubicin hydrochloride was brominated in the presence of propylene oxide and 14-bromodaunorubicin reacted with sodium maleimidobutyrate to yield doxorubicin 14-maleimidobutyrate. The latter was reacted with non-oxidized peptides to form doxorubicin-peptide conjugates.

IT 1069135-74-5
RL: PRPH (Prophetic)
(Method for the synthesis of anthracycline-peptide conjugates)

RN 1069135-74-5 HCAPLUS

CN INDEX NAME NOT YET ASSIGNED

Relative stereochemistry.

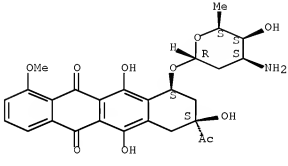


IT 20830-81-3, Daunorubicin 23541-50-6, Daunorubicin hydrochloride 50935-04-1 58957-92-9, Idarubicin
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis of anthracycline-peptide conjugates)

RN 20830-81-3 HCAPLUS

CN 5,12-Naphthacenedione, 8-acetyl-10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S,10S)- (CA INDEX NAME)

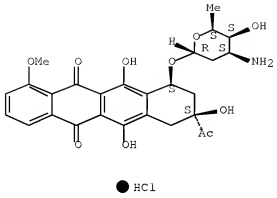
Absolute stereochemistry.



RN 23541-50-6 HCAPLUS

CN 5,12-Naphthacenedione, 8-acetyl-10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, hydrochloride (1:1), (8S,10S)- (CA INDEX NAME)

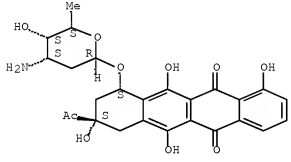
Absolute stereochemistry.



RN 50935-04-1 HCAPLUS

CN 5,12-Naphthacenedione, 8-acetyl-10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-1,6,8,11-tetrahydroxy-, (8S,10S)-(CA INDEX NAME)

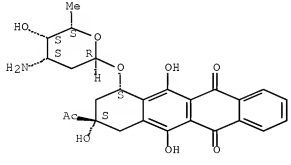
Absolute stereochemistry.



RN 58957-92-9 HCAPLUS

CN 5,12-Naphthacenedione, 9-acetyl-7-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxy-, (7S,9S)- (CA INDEX NAME)

Absolute stereochemistry.

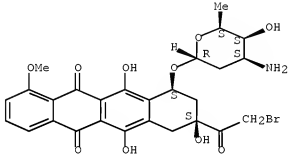


IT 65026-79-1P, 14 Bromodaunorubicin 121250-06-4P
652978-25-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of anthracycline-peptide conjugates)

RN 65026-79-1 HCAPLUS

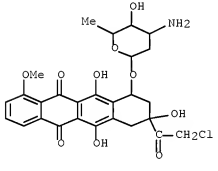
CN 5,12-Naphthacenedione, 10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-8-(2-bromoacetyl)-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.



RN 121250-06-4 HCAPLUS

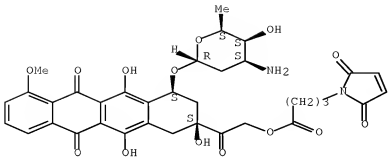
CN 5,12-Naphthacenedione, 10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-8-(2-chloroacetyl)-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S,10S)- (CA INDEX NAME)



RN 652978-25-1 HCAPLUS

CN 1H-Pyrrole-1-butanoic acid, 2,5-dihydro-2,5-dioxo-, 2-[(2S,4S)-4-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-1,2,3,4,6,11-hexahydro-2,5,12-trihydroxy-7-methoxy-6,11-dioxo-2-naphthacenyl]-2-oxoethyl ester (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 10 OF 20 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2002:755199 HCAPLUS Full-text
DOCUMENT NUMBER: 137:284323
TITLE: Enzyme-cleavable prodrug compounds
INVENTOR(S): Dubois, Vincent; Fernandez, Anne Marie; Gangwar, Sanjeev; Lewis, Evan; Lobl, Thomas J.; Nieder, Matthew H.; Pickford, Lesley B.; Trouet, Andre; Yarranton, Geoffrey T.
PATENT ASSIGNEE(S): Belg.
SOURCE: U.S. Pat. Appl. Publ., 86 pp., Cont.-in-part of Appl. No. PCT/US99/30393.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20020142955	A1	20021003	US 2001-879442	20010611
US 7425541	B2	20080916		
WO 2000033888	A2	20000615	WO 1999-US30393	19991210
WO 2000033888	A3	20011108		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:		
US 1998-111793P	P	19981211
US 1999-119312P	P	19990208
WO 1999-US30393	A2	19991210
US 2000-211887P	P	20000614
US 2001-290448P	P	20010511

OTHER SOURCE(S): MARPAT 137:284323

AB The prodrug of the invention is a modified form of a therapeutic agent and comprises a therapeutic agent, an oligopeptide, a stabilizing group and, optionally, a linker group. The prodrug is cleavable by the enzyme Thimet oligopeptidase, or TOP. Also disclosed are methods of designing prodrugs by

utilizing TOP-cleavable sequences within the conjugate and methods of treating patients with prodrugs of the invention.

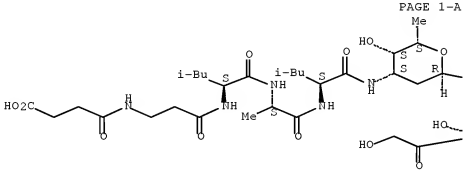
IT 274912-87-7P 274912-88-8P 274912-89-9P
RL: BSU (Biological study, unclassified); PNU (Preparation, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(thimet oligopeptidase-cleavable prodrug compds.)

RN 274912-87-7 HCAPLUS

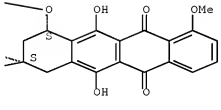
CN 5,12-Naphthacenedione, 10-[[3-[[N-(3-carboxy-1-oxopropyl)-β-alanyl-L-leucyl-L-alanyl-L-leucyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

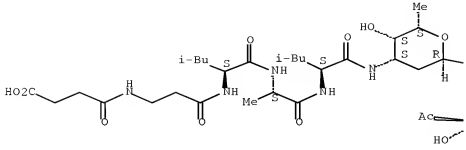


RN 274912-88-8 HCAPLUS

CN 5,12-Naphthacenedione, 8-acetyl-10-[[3-[[N-(3-carboxy-1-oxopropyl)-β-alanyl-L-leucyl-L-alanyl-L-leucyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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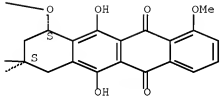
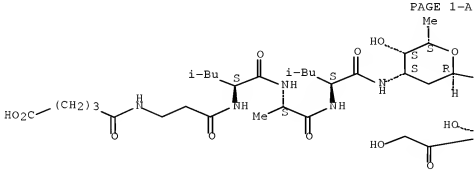


RN 274912-89-9 HCAPLUS

CN 5,12-Naphthacenedione, 10-[[3-[[N-(4-carboxy-1-oxobutyl)-β-alanyl-L-leucyl-L-alanyl-L-leucyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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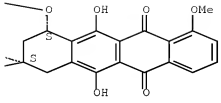


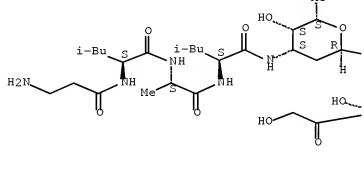
IT 177953-52-5P 274912-90-2P 274912-91-3P
274912-92-4P 274912-99-1P 274913-02-9P
274913-03-0P 274913-06-3P 274913-07-4P
464190-81-6P 464190-82-7P
RL: BSU (Biological study, unclassified); PNU (Preparation, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(thimet oligopeptidase-cleavable prodrug compds.)

RN 177953-52-5 HCAPLUS

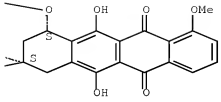
CN 5,12-Naphthacenedione, 10-[[3-[(β-alanyl-L-leucyl-L-alanyl-L-leucyl)amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, (8S,10S)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



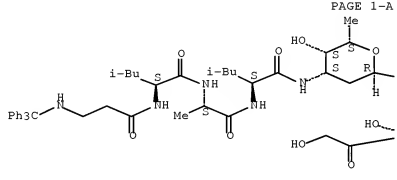
PAGE 1-B



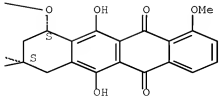
RN 274912-90-2 HCAPLUS
CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[[N-(triphenylmethyl)-β-alanyl-L-leucyl-L-alanyl-L-leucyl]amino]-α-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

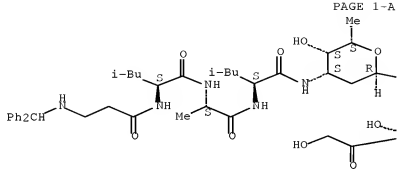


RN 274912-91-3 HCAPLUS
CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[[N-(diphenylmethyl)-

β-alanyl-L-leucyl-L-alanyl-L-leucyl]amino]-α-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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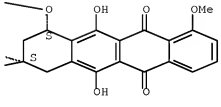
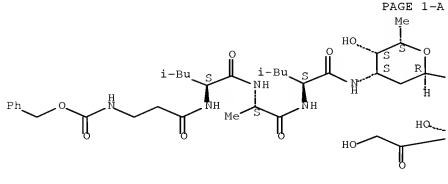


RN 274912-92-4 HCAPLUS

CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[[N-[(phenylmethoxy)carbonyl]-β-alanyl-L-leucyl-L-alanyl-L-leucyl]amino]-α-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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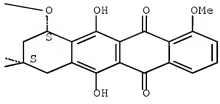
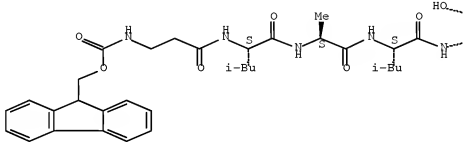


RN 274912-99-1 HCAPLUS
CN 5,12-Naphthacenedione, 8-acetyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-10-[[2,3,6-trideoxy-3-[[N-[(9H-fluoren-9-ylmethoxy)carbonyl]-β-alanyl-L-leucyl-L-alanyl-L-leucyl]amino]-α-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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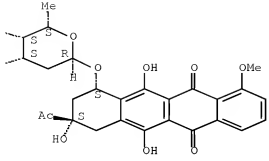


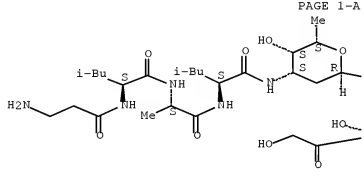
RN 274913-02-9 HCAPLUS
CN Propanoic acid, 2-hydroxy-, compd. with (8S,10S)-10-[[3-[(β-alanyl-L-leucyl-L-alanyl-L-leucyl)amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-5,12-naphthacenedione (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 177953-52-5
CMF C45 H61 N5 O15

Absolute stereochemistry.

PAGE 1-A



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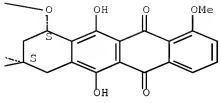


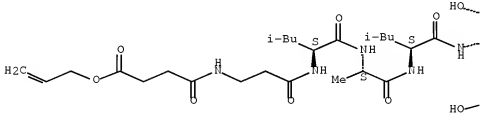
CM 2

CRN 50-21-5
CMF C3 H6 O3

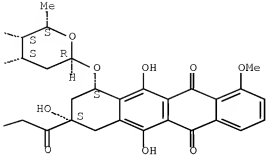
RN 274913-03-0 HCAPLUS
CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[[N-[1,4-dioxo-4-(2-propenyloxy)butyl]-β-alanyl-L-leucyl-L-alanyl-L-leucyl]amino]-α-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



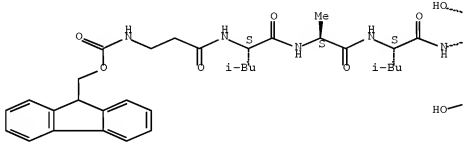
PAGE 1-B



RN 274913-06-3 HCAPLUS
CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[[N-[(9H-fluoren-9-ylmethoxy)carbonyl]-β-alanyl-L-leucyl-L-alanyl-L-leucyl]amino]-α-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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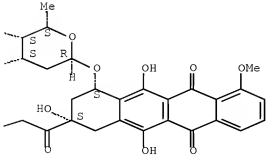
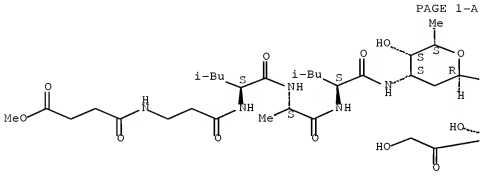


RN 274913-07-4 HCAPLUS
CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-

(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[[N-(4-methoxy-1,4-dioxobutyl)-β-alanyl-L-leucyl-L-alanyl-L-leucyl]amino]-α-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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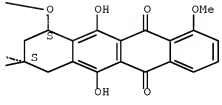
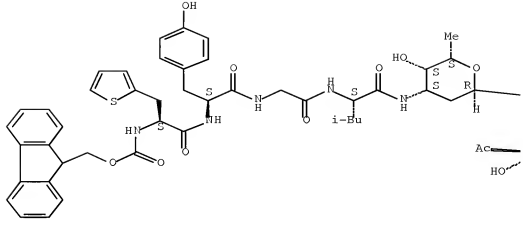


RN 464190-81-6 HCAPLUS

CN 5,12-Naphthacenedione, 8-acetyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-10-[[2,3,6-trideoxy-3-[[N-[(9H-fluoren-9-ylmethoxy)carbonyl]-3-(2-thienyl)-L-alanyl-L-tyrosylglycyl-L-leucyl]amino]-α-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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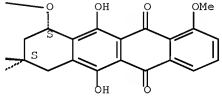
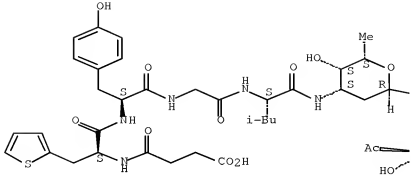


RN 464190-82-7 HCAPLUS
CN 5,12-Naphthacenedione, 8-acetyl-10-[[3-[[N-(3-carboxy-1-oxopropyl)-3-(2-thienyl)-L-alanyl-L-tyrosylglycyl-L-leucyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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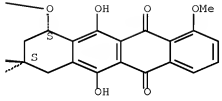
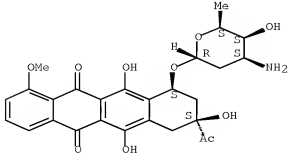


IT 20830-81-3, Daunorubicin 23214-92-8, Doxorubicin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thimet oligopeptidase-cleavable prodrug compds.)
RN 20830-81-3 HCAPLUS
CN 5,12-Naphthacenedione, 8-acetyl-10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S,10S)- (CA INDEX NAME)

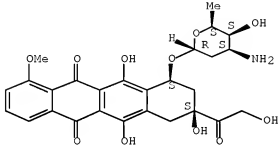
Absolute stereochemistry.



RN 23214-92-8 HCAPLUS

CN 5,12-Naphthacenedione, 10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 156 THERE ARE 156 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 11 OF 20 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2002:594708 HCAPLUS Full-text
DOCUMENT NUMBER: 137:150220
TITLE: Antitumor peptide conjugates
INVENTOR(S): Trouet, Andre; Dubois, Vincent
PATENT ASSIGNEE(S): Universite Catholique De Louvain, Belg.
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002060488	A1	20020808	WO 2002-EP951	20020130
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002229730	A1	20020812	AU 2002-229730	20020130
EP 1355675	A1	20031029	EP 2002-710820	20020130
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 20040097586	A1	20040520	US 2003-470466	20031222
PRIORITY APPLN. INFO.:			EP 2001-870017	A 20010130

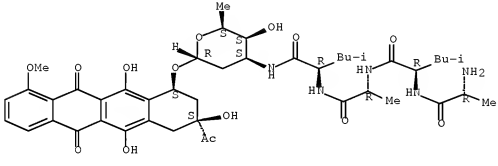
AB The invention is in particular related to compds. with the general formula A-B, which in the vicinity of tumor cells result in a pos. charged moiety B and an uncharged or neg. charged moiety A, whereby said moiety B is able to induce blood clotting by interacting with neg. charged heparin-like substances lining vascular endothelia and whereby the pos. charge is reversibly masked by the uncharged or neg. charged moiety A in order to prevent unspecific disseminated blood coagulation and toxicity. The polycation moiety B is able to induce blood clotting by interacting with neg. charged heparin-like substances lining vascular endothelia. The pos. charges of the B moiety within the prodrug are masked by the uncharged or neg. charged moiety A in order to prevent unspecific disseminated blood coagulation and toxicity. B is either a covalent assembly of pos. charged chemical groups or a pos. charged mol., which in aqueous solns. forms non-covalent polycations due to its propensity to form intermol. aggregates. E.g., the prodrug methoxy-PEG-Ala-Leu-Ala-Leu-D-Ala-D-Leu-D- Ala-D-Leu-DNR (DNR = daunorubicin) was prepared and the chemotherapeutic activity determined in exptl. tumor models.

IT 445235-10-9P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(antitumor peptide conjugates)

RN 445235-10-9 HCAPLUS

CN 5,12-Naphthacenedione, 8-acetyl-10-[[3-[(D-alanyl-D-leucyl-D-alanyl-D-leucyl)amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

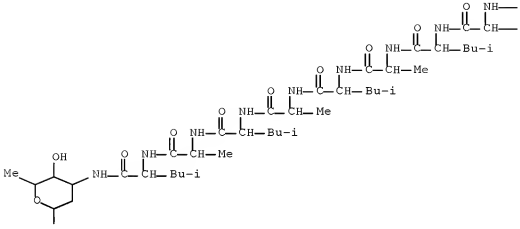


IT 445235-15-4P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(antitumor peptide conjugates)

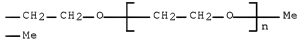
RN 445235-15-4 HCAPLUS

CN Poly(oxy-1,2-ethanediyl), α-methyl-ω-hydroxy-, 1''-ether with (8S,10S)-8-acetyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-10-[[2,3,6-trideoxy-3-[[N-(2-hydroxyethyl)-L-alanyl-L-leucyl-L-alanyl-L-leucyl-D-alanyl-D-leucyl-D-alanyl-D-leucyl]amino]-α-L-lyxo-hexopyranosyl]oxy]-5,12-naphthacenedione (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 1-B



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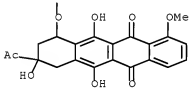
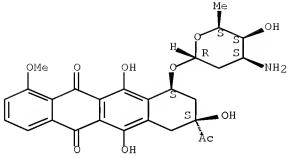


IT 20830-81-3, Daunorubicin
RL: RCT (Reactant); RACT (Reactant or reagent)
(antitumor peptide conjugates)
RN 20830-81-3 HCAPLUS
CN 5,12-Naphthacenedione, 8-acetyl-10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S,10S)- (CA INDEX NAME)

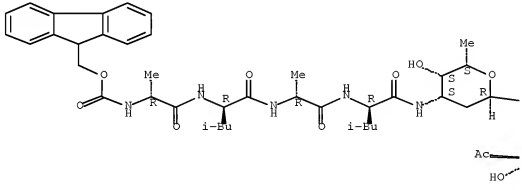
Absolute stereochemistry.

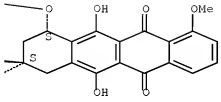


IT 445235-12-1P 445235-13-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(antitumor peptide conjugates)
RN 445235-12-1 HCAPLUS
CN 5,12-Naphthacenedione, 8-acetyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-10-[[2,3,6-trideoxy-3-[[N-[(9H-fluoren-9-ylmethoxy)carbonyl]-D-alanyl-D-leucyl-D-alanyl-D-leucyl]amino]-α-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



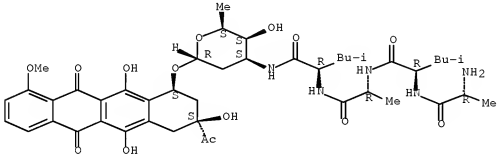


RN 445235-13-2 HCAPLUS
CN 5,12-Naphthacenedione, 8-acetyl-10-[[3-[(D-alanyl-D-leucyl-D-alanyl-D-leucyl)amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S,10S)-, mono(2-hydroxypropanoate) (salt) (9CI) (CA INDEX NAME)

CM 1

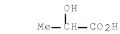
CRN 445235-10-9
CMF C45 H61 N5 O14

Absolute stereochemistry.



CM 2

CRN 50-21-5
CMF C3 H6 O3



REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 12 OF 20 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2002:323079 HCAPLUS Full-text
DOCUMENT NUMBER: 137:241802
TITLE: CPI-0004Na, a new extracellularly tumor-activated prodrug of Doxorubicin: in vivo toxicity, activity, and tissue distribution confirm tumor cell selectivity
AUTHOR(S): Dubois, Vincent; Dasnois, Luc; Lebtahi, Karim; Collot, Francoise; Heylen, Nathalie; Havaux, Nathalie; Fernandez, Anne-Marie; Lobl, Thomas J.; Oliyai, Cecilia; Nieder, Matthew; Shochat, Dan; Yarranton, Geoffrey T.; Trouet, Andre
CORPORATE SOURCE: Universite Catholique de Louvain, Laboratory of Cell Biology, Louvain-la-Neuve, B-1348, Belg.
SOURCE: Cancer Research (2002), 62(8), 2327-2331
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The search for cancer therapies that are more selective for tumor cells and spare normal sensitive cells has been very active for at least 20 yr. The extracellularly tumor-activated peptidic prodrug of doxorubicin (Dox) CPI-0004Na (N-succinyl-β-alanyl-L-leucyl-L-alanyl-L-leucyl-Dox) is potentially such a treatment. Here, we report the results of lethality studies performed with this compound in the mouse, showing that it is up to 4.6 times less toxic than Dox·HCl by the i.v. route and up to 16.2 times after i.p. administration. Pharmacokinetics and tissue distribution data indicate that this reduced toxicity is attributable to a lower uptake of Dox in normal tissues after treatment with CPI-0004Na than after the administration of an equimolar dose of Dox·HCl. For example, heart exposure to Dox is reduced > 10-fold. Because of this reduced toxicity, higher doses of CPI-0004Na than of the parent drug could be used to treat nude mice bearing s.c. human breast (MCF-7/6) and colon (LS-174-T and CXF-280/10) tumors. In all three models, the prodrug showed a much improved efficacy as compared with Dox·HCl. Particularly, LS-174-T tumors that do not respond to Dox were inhibited by 68% after treatment with CPI-0004Na. Tissue distribution studies performed with MCF-7/6 tumor-bearing nude mice and comparing CPI-0004Na and Dox·HCl confirmed that the improved activity of the prodrug is actually the result of selective generation and uptake of Dox at the tumor site. Dox levels in tumor tissue were 2-fold higher after treatment with CPI-0004Na than after treatment with an equimolar dose of Dox·HCl, whereas normal tissue levels were reduced 1.4-29-fold.

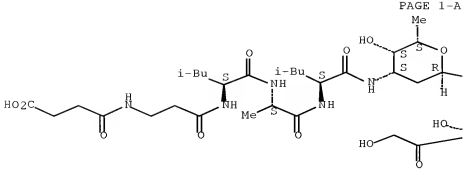
IT 274912-87-7
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in vivo toxicity, activity, and tissue distribution confirm tumor cell selectivity of CPI-0004Na)

RN 274912-87-7 HCAPLUS

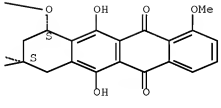
CN 5,12-Naphthacenedione, 10-[[3-[[N-(3-carboxy-1-oxopropyl)-β-alanyl-L-leucyl-L-alanyl-L-leucyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

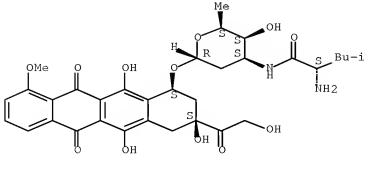


PAGE 1-B



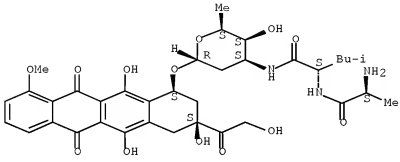
IT 70774-25-3, N-L-Leucyl-doxorubicin 177953-54-7
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(in vivo toxicity, activity, and tissue distribution confirm tumor cell selectivity of CPI-0004Na)
RN 70774-25-3 HCAPLUS
CN 5,12-Naphthacenedione, 10-[[3-[[(2S)-2-amino-4-methyl-1-oxopentyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.



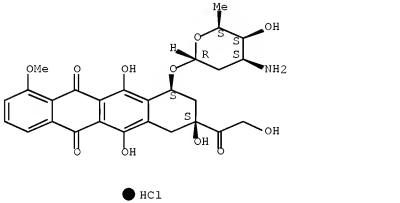
RN 177953-54-7 HCAPLUS
CN 5,12-Naphthacenedione, 10-[[3-[(L-alanyl-L-leucyl)amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.



IT 25316-40-9, Doxorubicin hydrochloride
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in vivo toxicity, activity, and tissue distribution confirm tumor cell selectivity of CPI-0004Na)
RN 25316-40-9 HCAPLUS
CN 5,12-Naphthacenedione, 10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, hydrochloride (1:1), (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.



● HCl

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 13 OF 20 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2002:157495 HCAPLUS Full-text
DOCUMENT NUMBER: 136:205412
TITLE: Oligopeptide-based prodrugs activated by plasmin and their use in cancer chemotherapy

INVENTOR(S): Trouet, Andre; Dubois, Vincent; Passioukov, Alexandre
PATENT ASSIGNEE(S): Coulter Pharmaceutical, Inc., USA
SOURCE: PCT Int. Appl., 67 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002015700	A1	20020228	WO 2001-US26476	20010823
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2001086727	A	20020304	AU 2001-86727	20010823
US 20040171562	A1	20040902	US 2003-362958	20031031
US 7402556	B2	20080722		

PRIORITY APPLN. INFO.: US 2000-227686P P 20000824
WO 2001-US26476 W 20010823

OTHER SOURCE(S): MARPAT 136:205412

AB A prodrug, cleavable by plasmin, comprises a therapeutic agent capable of entering a target cell, e.g., a tumor or inflammatory cell, an oligopeptide having a plasmin peptide substrate of 2-4 amino acids and mono- or di-peptide linkage, a stabilizing group and, optionally, a linker group. Also disclosed are methods of making and using the prodrug compds. For example, the activity of D-Ala-Leu-Lys-Leu-Leu-doxorubicin (I) (preparation given) was evaluated in the B16-B16 murine melanoma model. The mice receiving the prodrug did not show any important weight loss during the experiment and no clin. signs of toxicity were observed At the same time, the drug had a marked effect on the metastatic growth. At 34.5 μmol/kg, I reduced the spread of lung metastases with a decrease of the ratio of the surface occupied by B16-B16 colonies to the non-affected one to 8.2±1.8% (P<0.01), compared to 45.7±12.6% and 44.0±6.3% for non-treated and doxorubicin (5.2 μmol/kg)-treated animals. The same prodrug at 69.0 μmol/kg provided 1.5±0.6% of surface affected.

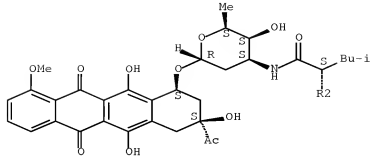
IT 401600-69-9P 401600-70-2P 401600-71-3P
401600-72-4P
RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of action); PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(oligopeptide-based prodrugs activated by plasmin for chemotherapy)

RN 401600-69-9 HCAPLUS

CN 5,12-Naphthacenedione, 8-acetyl-10-[[3-[(D-alanyl-L-leucyl-L-lysyl-L-leucyl)amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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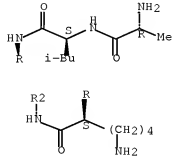

RN 401600-70-2 HCAPLUS
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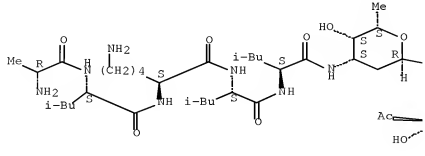
Absolute stereochemistry.

PAGE 1-A



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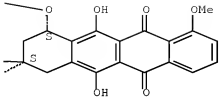
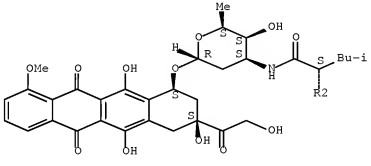


RN 401600-71-3 HCAPLUS
CN 5,12-Naphthacenedione, 10-[[3-[(D-alanyl-L-leucyl-L-lysyl-L-leucyl)amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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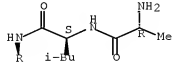
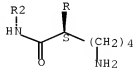
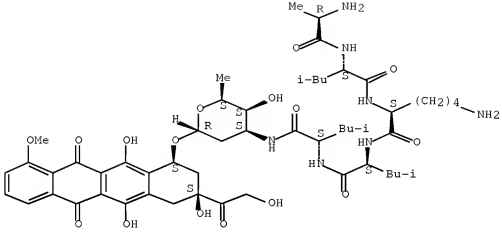




RN 401600-72-4 HCAPLUS
CN 5,12-Naphthacenedione, 10-[[3-[(D-alanyl-L-leucyl-L-lysyl-L-leucyl-L-leucyl)amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-

tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

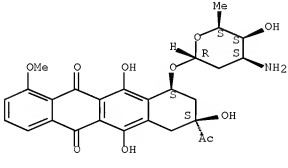


IT 20830-81-3 23214-92-8
RL: BSU (Biological study, unclassified); RCT (Reactant); BIOL (Biological study); RACT (Reactant or reagent)
(oligopeptide-based prodrugs activated by plasmin for chemotherapy)

RN 20830-81-3 HCAPLUS

CN 5,12-Naphthacenedione, 8-acetyl-10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S,10S)- (CA INDEX NAME)

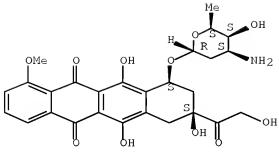
Absolute stereochemistry.



RN 23214-92-8 HCAPLUS

CN 5,12-Naphthacenedione, 10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.

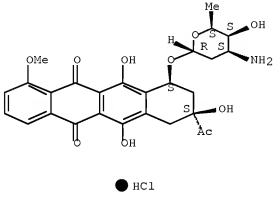


IT 23541-50-6, Daunorubicin hydrochloride 23828-85-5
25316-40-9, Doxorubicin hydrochloride 70722-93-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(oligopeptide-based prodrugs activated by plasmin for chemotherapy)

RN 23541-50-6 HCAPLUS

CN 5,12-Naphthacenedione, 8-acetyl-10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, hydrochloride (1:1), (8S,10S)- (CA INDEX NAME)

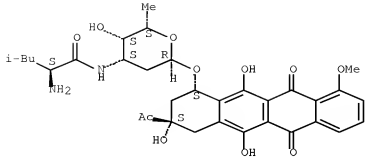
Absolute stereochemistry.



RN 23828-85-5 HCAPLUS

CN 5,12-Naphthacenedione, 8-acetyl-10-[[3-[[(2S)-2-amino-4-methyl-1-oxopentyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, monohydrochloride, (8S,10S)-(9CI) (CA INDEX NAME)

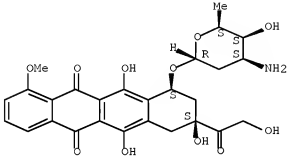
Absolute stereochemistry.



● HCl

RN 25316-40-9 HCAPLUS
CN 5,12-Naphthacenedione, 10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, hydrochloride (1:1), (8S,10S)- (CA INDEX NAME)

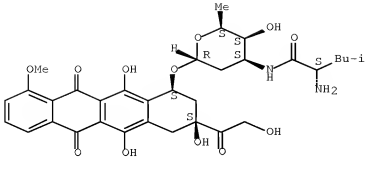
Absolute stereochemistry.



● HCl

RN 70722-93-9 HCAPLUS
CN 5,12-Naphthacenedione, 10-[[3-[[(2S)-2-amino-4-methyl-1-oxopentyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, monohydrochloride, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 14 OF 20 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2002:10314 HCAPLUS Full-text
DOCUMENT NUMBER: 136:86054
TITLE: Tripeptide prodrug compounds
INVENTOR(S): Bebbington, Christopher R.; Dubois, Vincent; Gangwar, Sanjeev; Lobl, Thomas J.; Nieder, Matthew H.; Pickford, Leslie B.; Trouet, Andre; Yarranton, Geoffrey T.
PATENT ASSIGNEE(S): Corixa Corporation, USA
SOURCE: PCT Int. Appl., 102 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002000263	A2	20020103	WO 2001-US40925	20010611
WO 2002000263	A3	20020815		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2411545	A1	20020103	CA 2001-2411545	20010611
EP 1294403	A2	20030326	EP 2001-942249	20010611
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004501875	T	20040122	JP 2002-505044	20010611
AU 2001275525	B2	20070426	AU 2001-275525	20010611
US 20030181359	A1	20030925	US 2002-311519	20021213
US 7214663	B2	20070508		
US 20070275903	A1	20071129	US 2007-728771	20070327

PRIORITY APPLN. INFO.: US 2000-212880P P 20000614
WO 2001-US40925 W 20010611
US 2002-311519 A1 20021213

OTHER SOURCE(S): CASREACT 136:86054; MARPAT 136:86054

AB The prodrug of the invention is a modified form of a therapeutic agent and comprises a therapeutic agent, an oligopeptide AA3-AA2-AA1 (AA1 is leucine, phenylalanine, isoleucine, alanine, glycine, tyrosine, 2-naphthylalanine, or serine; AA2 is alanine, leucine, tyrosine, glycine, serine, 3-pyridylalanine, 2-thienylalanine, aminoisobutyric acid, threonine, or phenylalanine; AA3 is leucine, sarcosine, tyrosine, phenylalanine, p-chloro- or p-nitrophenylalanine, valine, norleucine, norvaline, phenylglycine, tryptophan, tetrahydroisoquinoline-3-carboxylic acid, 3-pyridylalanine, alanine, glycine, 2-thienylalanine, methionine, or proline), a stabilizing group and, optionally, a linker group. The prodrug is cleavable by a trouase enzyme such as Thimet oligopeptidase. Thus, Suc-Leu-Ala-Leu-Dox (Suc = succinic acid residue, Dox = doxorubicin residue), prepared by conjugation of doxorubicin hydrochloride with Fmoc-Leu-Ala-Leu-OH, deprotection, and acylation with succinic anhydride, showed tumor-activated prodrug activity on LNCaP, HT-29 and PC-3 cells of 0.016, 0.052, and 0.075 μM, resp. Suc-Leu-Ala-Leu-Dox is better tolerated in vivo than is doxorubicin.

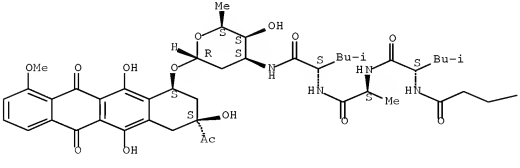
IT 177953-67-2P 274912-67-7P 380861-69-8P
380861-87-0P 385449-21-8P 385449-22-9P
385449-23-0P 385449-24-1P 385449-25-2P
385449-26-3P 385449-27-4P 385449-28-5P
385449-29-6P 385449-30-9P 385449-31-0P
385449-32-1P 385449-33-2P 385449-34-3P
385449-35-4P 385449-36-5P 385449-37-6P
385449-38-7P 385449-41-2P 385449-42-3P
385449-43-4P 385449-44-5P 385449-45-6P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(tripeptide prodrug compds.)

RN 177953-67-2 HCAPLUS

CN 5,12-Naphthacenedione, 8-acetyl-10-[[3-[[N-(3-carboxy-1-oxopropyl)-L-leucyl-L-alanyl-L-leucyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



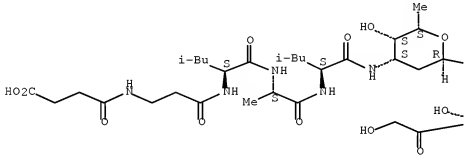
PAGE 1-B

RN 274912-87-7 HCAPLUS

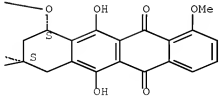
CN 5,12-Naphthacenedione, 10-[[3-[[N-(3-carboxy-1-oxopropyl)-β-alanyl-L-leucyl-L-alanyl-L-leucyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

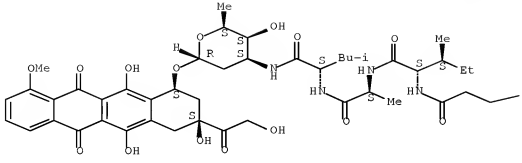


RN 380861-69-8 HCAPLUS

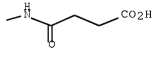
CN 5,12-Naphthacenedione, 10-[[3-[[N-(3-carboxy-1-oxopropyl)-β-alanyl-L-isoleucyl-L-alanyl-L-leucyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



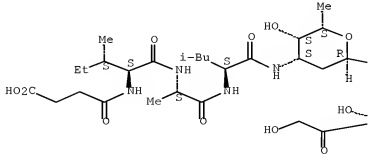
PAGE 1-B



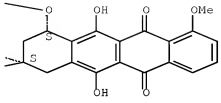
RN 380861-87-0 HCAPLUS
CN 5,12-Naphthacenedione, 10-[[3-[[N-(3-carboxy-1-oxopropyl)-L-isoleucyl-L-alanyl-L-leucyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



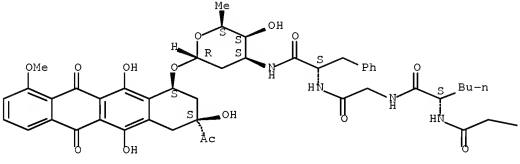
PAGE 1-B



RN 385449-21-8 HCAPLUS
CN 5,12-Naphthacenedione, 8-acetyl-10-[[3-[[N-(3-carboxy-1-oxopropyl)-L-norleucylglycyl-L-phenylalanyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



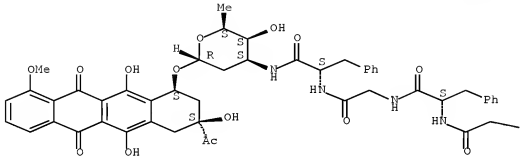
PAGE 1-B

RN 385449-22-9 HCAPLUS
CN 5,12-Naphthacenedione, 8-acetyl-10-[[3-[[N-(3-carboxy-1-oxopropyl)-L-phenylalanylglycyl-L-phenylalanyl]amino]-2,3,6-trideoxy-α-L-lyxo-

hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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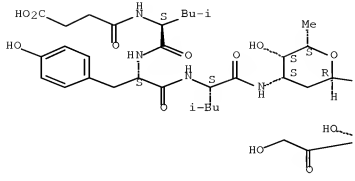
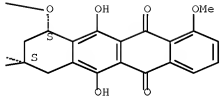
RN 385449-23-0 HCAPLUS
CN 5,12-Naphthacenedione, 10-[[3-[[N-(3-carboxy-1-oxopropyl)-L-leucyl-L-tyrosyl-L-leucyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



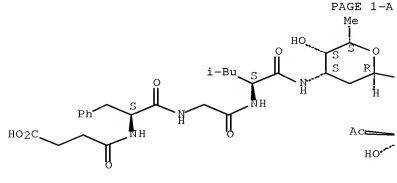
PAGE 1-B



RN 385449-24-1 HCAPLUS
CN 5,12-Naphthacenedione, 8-acetyl-10-[[3-[[N-(3-carboxy-1-oxopropyl)-L-phenylalanylglycyl-L-leucyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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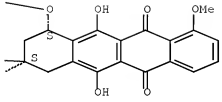
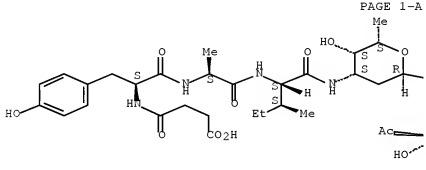


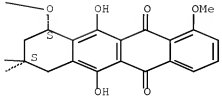
RN 385449-25-2 HCAPLUS
CN 5,12-Naphthacenedione, 8-acetyl-10-[[3-[[N-(3-carboxy-1-oxopropyl)-L-tyrosyl-L-alanyl-L-isoleucyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



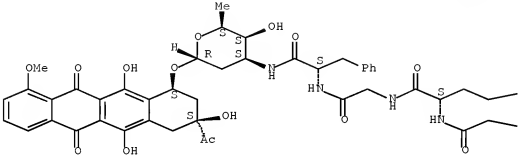
PAGE 1-B



RN 385449-26-3 HCAPLUS
CN 5,12-Naphthacenedione, 8-acetyl-10-[[3-[[N-(3-carboxy-1-oxopropyl)-L-methionylglycyl-L-phenylalanyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

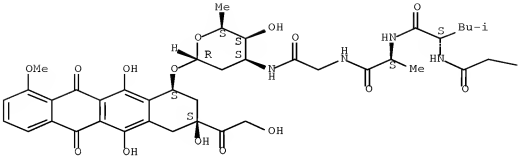


PAGE 1-B

RN 385449-27-4 HCAPLUS
CN 5,12-Naphthacenedione, 10-[[3-[[N-(3-carboxy-1-oxopropyl)-L-leucyl-L-alanylglycyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

RN 385449-28-5 HCAPLUS
CN 5,12-Naphthacenedione, 8-acetyl-10-[[3-[[N-(3-carboxy-1-oxopropyl)-L-methionylglycyl-L-isoleucyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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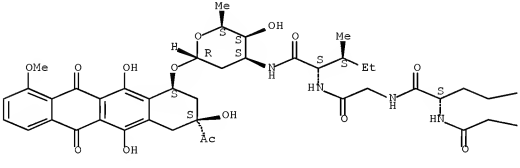
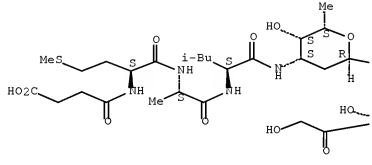


PAGE 1-B

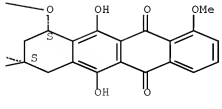
RN 385449-29-6 HCAPLUS
CN 5,12-Naphthacenedione, 10-[[3-[[N-(3-carboxy-1-oxopropyl)-L-methionyl-L-alanyl-L-leucyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

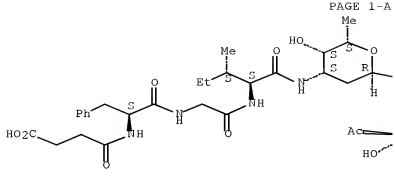


RN 385449-30-9 HCAPLUS
CN 5,12-Naphthacenedione, 8-acetyl-10-[[3-[[N-(3-carboxy-1-oxopropyl)-L-phenylalanylglycyl-L-isoleucyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-,

(8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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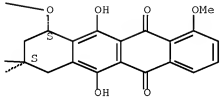

RN 385449-31-0 HCAPLUS
CN 5,12-Naphthacenedione, 8-acetyl-10-[[3-[[N-(3-carboxy-1-oxopropyl)-L-methionylglycyl-L-leucyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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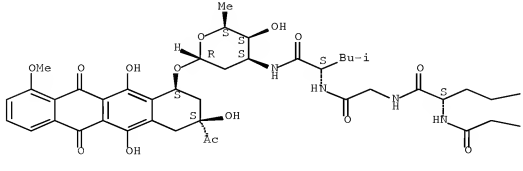

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RN 385449-32-1 HCAPLUS
CN 5,12-Naphthacenedione, 10-[[3-[[N-(3-carboxy-1-oxopropyl)-L-leucyl-L-alanyl-L-leucyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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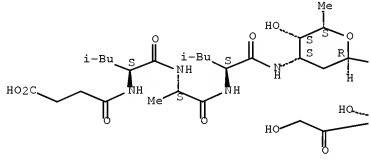
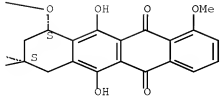


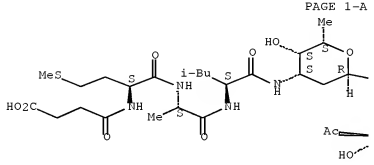
PAGE 1-B



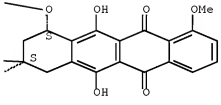
RN 385449-33-2 HCAPLUS
CN 5,12-Naphthacenedione, 8-acetyl-10-[[3-[[N-(3-carboxy-1-oxopropyl)-L-methionyl-L-alanyl-L-leucyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



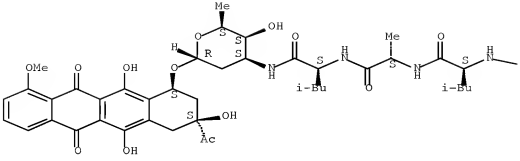
PAGE 1-B



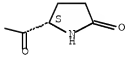
RN 385449-34-3 HCAPLUS
CN 5,12-Naphthacenedione, 8-acetyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-10-[[2,3,6-trideoxy-3-[(5-oxo-L-prolyl-L-leucyl-L-alanyl-L-leucyl)amino]-α-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



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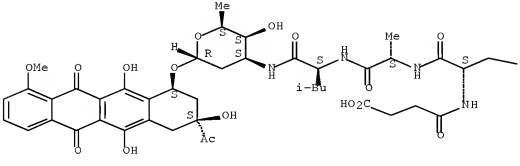
CN 5,12-Naphthacenedione, 8-acetyl-10-[[3-[[N-(3-carboxy-1-oxopropyl)-L-tyrosyl-L-alanyl-L-leucyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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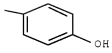
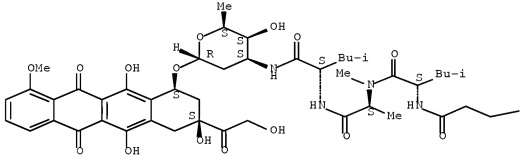


RN 385449-36-5 HCAPLUS
CN 5,12-Naphthacenedione, 10-[[3-[[N-(3-carboxy-1-oxopropyl)-L-leucyl-N-methyl-L-alanyl-L-leucyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

RN 385449-37-6 HCAPLUS
CN 5,12-Naphthacenedione, 10-[[3-[[N-(3-carboxy-1-oxopropyl)-L-isoleucyl-L-prolyl-L-leucyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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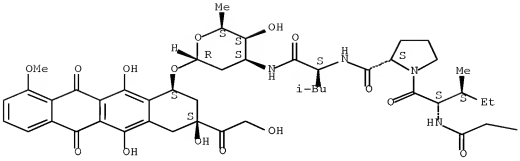

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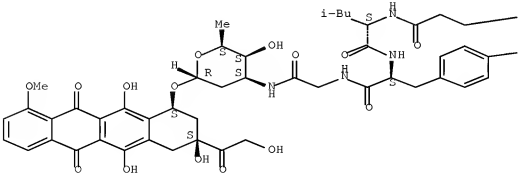
RN 385449-38-7 HCAPLUS
CN 5,12-Naphthacenedione, 10-[[3-[[N-(3-carboxy-1-oxopropyl)-L-leucyl-L-tyrosylglycyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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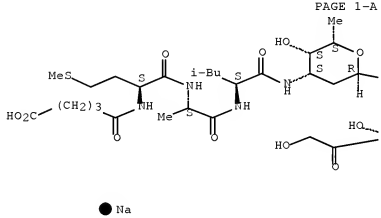
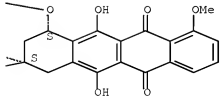
RN 385449-41-2 HCAPLUS
CN 5,12-Naphthacenedione, 10-[[3-[[N-(4-carboxy-1-oxobutyl)-L-methionyl-L-alanyl-L-leucyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, monosodium salt, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



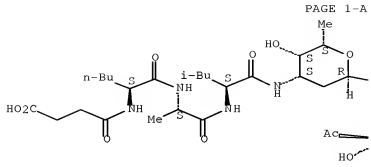
PAGE 1-B



RN 385449-42-3 HCAPLUS
CN 5,12-Naphthacenedione, 8-acetyl-10-[[3-[[N-(3-carboxy-1-oxopropyl)-L-norleucyl-L-alanyl-L-leucyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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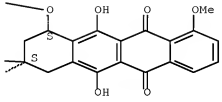
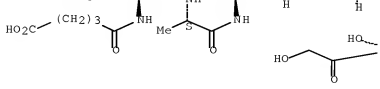


RN 385449-43-4 HCAPLUS
CN 5,12-Naphthacenedione, 10-[[3-[[N-(4-carboxy-1-oxobutyl)-L-methionyl-L-alanyl-L-leucyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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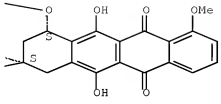
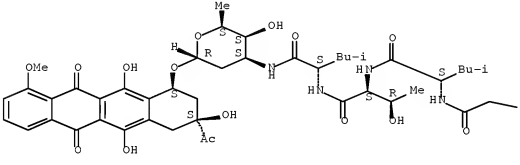


RN 385449-44-5 HCAPLUS
CN 5,12-Naphthacenedione, 8-acetyl-10-[[3-[[N-(3-carboxy-1-oxopropyl)-L-leucyl-L-threonyl-L-leucyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



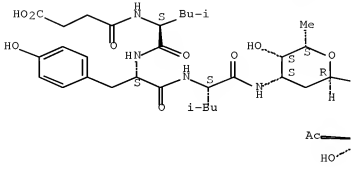
PAGE 1-B

RN 385449-45-6 HCAPLUS
CN 5,12-Naphthacenedione, 8-acetyl-10-[[3-[[N-(3-carboxy-1-oxopropyl)-L-leucyl-L-tyrosyl-L-leucyl]amino]-2,3,6-trideoxy-α-L-lyxo-

hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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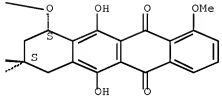
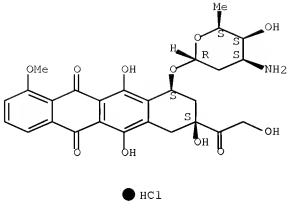


IT 25316-40-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(tripeptide prodrug compds.)
RN 25316-40-9 HCAPLUS
CN 5,12-Naphthacenedione, 10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, hydrochloride (1:1), (8S,10S)- (CA INDEX NAME)

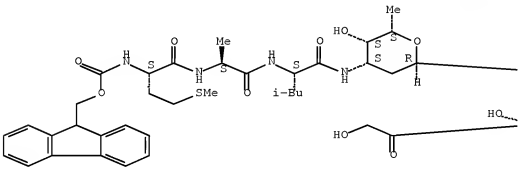
Absolute stereochemistry.

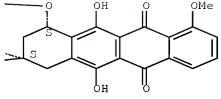


IT 385449-40-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(tripeptide prodrug compds.)
RN 385449-40-1 HCAPLUS
CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[[N-[(9H-fluoren-9-ylmethoxy)carbonyl]-L-methionyl-L-alanyl-L-leucyl]amino]-α-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

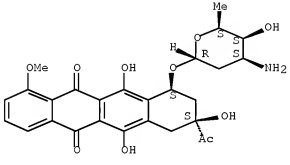
PAGE 1-A





IT 20830-81-3, Daunorubicin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tripeptide prodrug compds.)
RN 20830-81-3 HCAPLUS
CN 5,12-Naphthacenedione, 8-acetyl-10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 15 OF 20 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2001:923644 HCAPLUS Full-text
DOCUMENT NUMBER: 136:58787
TITLE: Enzyme-cleavable prodrug compounds
INVENTOR(S): Nieder, Matthew H.; Dubois, Vincent; Gangwar, Sanjeev; Lobl, Thomas J.; Pickford, Leslie B.; Trouet, Andre; Yarranton, Geoffrey T.
PATENT ASSIGNEE(S): Corixa Corporation, USA
SOURCE: PCT Int. Appl., 159 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2001095945 A2 20011220 WO 2001-US18903 20010611
WO 2001095945 A3 20020815
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
CA 2411660 A1 20011220 CA 2001-2411660 20010611
EP 1294405 A2 20030326 EP 2001-950291 20010611
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
JP 2004510703 T 20040408 JP 2002-510122 20010611
AU 2001271301 B2 20060831 AU 2001-271301 20010611
PRIORITY APPLN. INFO.: US 2000-211887P P 20000614
US 2001-290448P P 20010511
WO 2001-US18903 W 20010611

OTHER SOURCE(S): MARPAT 136:58787

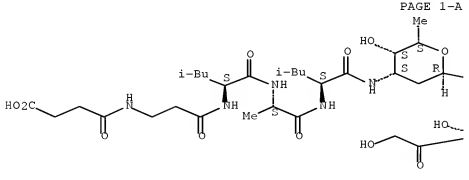
AB The prodrug of the invention is a modified form of a therapeutic agent and comprises a therapeutic agent, an oligopeptide, a stabilizing group and, optionally, a linker group. The prodrug is cleavable by the enzyme, thimet oligopeptidase (TOP). Also disclosed are methods of designing prodrugs by utilizing TOP-cleavage sequences within the conjugate and methods of treating patients with prodrugs of the invention.

IT 274912-87-7P 274912-88-8P 274912-89-9P
RL: PAC (Pharmacological activity); PNU (Preparation, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(enzyme-cleavable prodrug compds.)

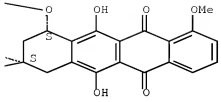
RN 274912-87-7 HCAPLUS

CN 5,12-Naphthacenedione, 10-[[3-[[N-(3-carboxy-1-oxopropyl)-β-alanyl-L-leucyl-L-alanyl-L-leucyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.



PAGE 1-B

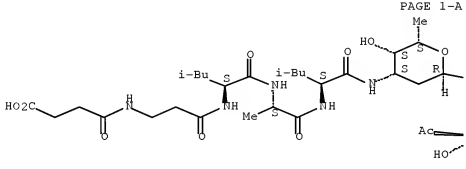


RN 274912-88-8 HCAPLUS

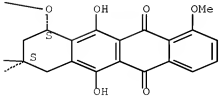
CN 5,12-Naphthacenedione, 8-acetyl-10-[[3-[[N-(3-carboxy-1-oxopropyl)-β-alanyl-L-leucyl-L-alanyl-L-leucyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



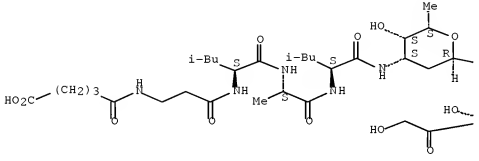
RN 274912-89-9 HCAPLUS

CN 5,12-Naphthacenedione, 10-[[3-[[N-(4-carboxy-1-oxobutyl)-β-alanyl-L-

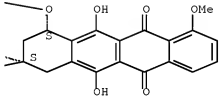
leucyl-L-alanyl-L-leucyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

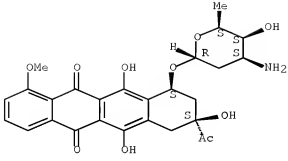


IT 20830-81-3, Daunorubicin 23214-92-8, Doxorubicin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(enzyme-cleavable prodrug compds.)

RN 20830-81-3 HCAPLUS

CN 5,12-Naphthacenedione, 8-acetyl-10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S,10S)- (CA INDEX NAME)

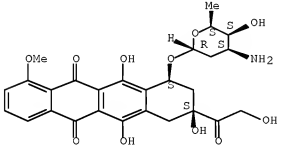
Absolute stereochemistry.



RN 23214-92-8 HCAPLUS

CN 5,12-Naphthacenedione, 10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 16 OF 20 HCAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2001:885823 HCAPLUS Full-text

DOCUMENT NUMBER: 136:42834

TITLE: Tumor activated prodrug compounds

INVENTOR(S): Trouet, Andre; Dubois, Vincent; Oronsky, Arnold

PATENT ASSIGNEE(S): Universite Catholique De Louvain, Belg.

SOURCE: PCT Int. Appl., 74 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001091798	A2	20011206	WO 2001-EP6106	20010529
WO 2001091798	A3	20021205		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,

SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2408103	A1	20011206	CA 2001-2408103		20010529
EP 1286700	A2	20030305	EP 2001-957808		20010529
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
JP 2003534387 T		20031118	JP 2001-587810		20010529
US 20040014652	A1	20040122	US 2003-296954		20030616
PRIORITY APPLN. INFO.:			US 2000-208996P	P	20000601
			EP 2000-870130	A	20000615
			EP 2000-870306	A	20001218
			WO 2001-EP6106	W	20010529

OTHER SOURCE(S): MARPAT 136:42834

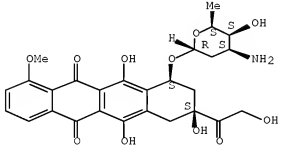
AB The invention is directed to novel prodrug compds., compns. comprising the prodrugs, methods of making and using them. The prodrugs comprise a biol. active entity linked to a masking moiety via a linking moiety. The prodrug compds. are selectively activated at or near target cells and display lower toxicity and possibly a longer in vivo or serum half-life than the corresponding naked biol. active entity. A IGF-1 antagonist is used to prepare a dual prodrug with doxorubicin. For the dual prodrug, conjugation takes place at the carboxyterminus of the antagonist rather than on its free N-terminal amino group. The in vivo toxicity of the dual prodrug is evaluated, and its chemotherapeutic activity is compared to that of Dox and of the IGF-1 antagonist, alone or in combination.

IT 23214-92-8D, Doxorubicin, prodrugs
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tumor activated prodrug compds.)

RN 23214-92-8 HCAPLUS

CN 5,12-Naphthacenedione, 10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.



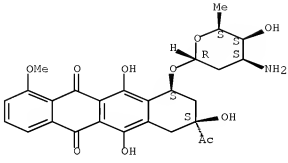
IT 20830-81-3D, Daunorubicin, prodrugs
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tumor activated prodrug compds.)

RN 20830-81-3 HCAPLUS

CN 5,12-Naphthacenedione, 8-acetyl-10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-,

(8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 17 OF 20 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2001:653068 HCAPLUS Full-text
DOCUMENT NUMBER: 135:362468
TITLE: N-succinyl-(β-alanyl-L-leucyl-L-alanyl-L-leucyl)doxorubicin: an extracellularly tumor-activated prodrug devoid of intravenous acute toxicity
AUTHOR(S): Fernandez, Anne-Marie; Van derpoorten, Kim; Dasnois, Luc; Lebtahi, Karim; Dubois, Vincent; Lobl, Thomas J.; Gangwar, Sanjeev; Oliyai, Cecilia; Lewis, Evan R.; Shochat, Dan; Trouet, Andre
CORPORATE SOURCE: Laboratory of Cell Biology, Universite Catholique de Louvain, Louvain-la-Neuve, B-1348, Belg.
SOURCE: Journal of Medicinal Chemistry (2001), 44(22), 3750-3753
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

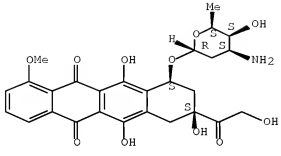
AB I.v. administration of N-(β-alanyl-L-leucyl-L-alanyl-L- leucyl)doxorubicin induces an acute toxic reaction, killing animals in a few minutes. This results from its pos. charge at physiol. pH combined with its propensity to form large aggregates in aqueous solns. Neg. charged N-capped versions of N-(β-alanyl-L-leucyl-L-alanyl-L- leucyl)doxorubicin such as the succinyl derivative can be administered by the i.v. route at more than 10 times the LD50 of doxorubicin without inducing the acute toxic reaction, and they are active in vivo.

IT 23214-92-8, Doxorubicin
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(N-succinyl-(β-alanyl-L-leucyl-L-alanyl-L-leucyl)doxorubicin: an extracellularly tumor-activated prodrug devoid of i.v. acute toxicity)

RN 23214-92-8 HCAPLUS

CN 5,12-Naphthacenedione, 10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.



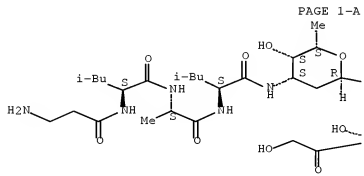
IT 274913-02-9P 372491-73-1P
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(N-succinyl-(β-alanyl-L-leucyl-L-alanyl-L-leucyl)doxorubicin: an extracellularly tumor-activated prodrug devoid of i.v. acute toxicity)
RN 274913-02-9 HCAPLUS
CN Propanoic acid, 2-hydroxy-, compd. with (8S,10S)-10-[[3-[(β-alanyl-L-leucyl-L-alanyl-L-leucyl)amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-5,12-naphthacenedione (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 177953-52-5
CMF C45 H61 N5 O15

Absolute stereochemistry.

PAGE 1-A



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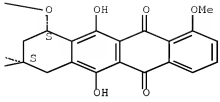


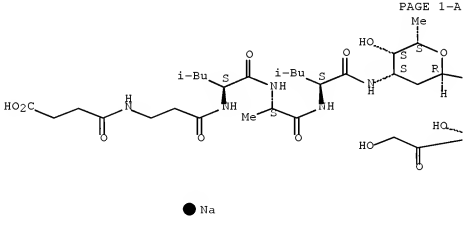
CM 2

CRN 50-21-5
CMF C3 H6 O3

RN 372491-73-1 HCAPLUS
CN 5,12-Naphthacenedione, 10-[[3-[[N-(3-carboxy-1-oxopropyl)-β-alanyl-L-leucyl-L-alanyl-L-leucyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, monosodium salt, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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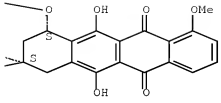
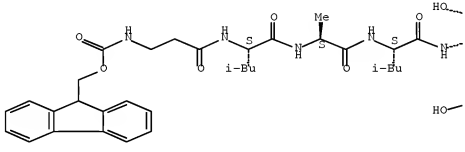
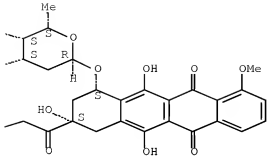


IT 274913-06-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(N-succinyl-(β-alanyl-L-leucyl-L-alanyl-L-leucyl)doxorubicin: an extracellularly tumor-activated prodrug devoid of i.v. acute toxicity)
RN 274913-06-3 HCAPLUS
CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[[N-[(9H-fluoren-9-ylmethoxy)carbonyl]-β-alanyl-L-leucyl-L-alanyl-L-leucyl]amino]-α-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A





REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

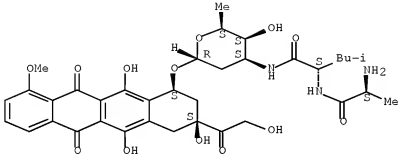
L36 ANSWER 18 OF 20 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2001:295889 HCAPLUS Full-text
DOCUMENT NUMBER: 135:116741
TITLE: Extracellularly tumor-activated prodrugs for the selective chemotherapy of cancer: application to doxorubicin and preliminary in vitro and in vivo studies
AUTHOR(S): Trouet, Andre; Passioukov, Alexandre; Van derpoorten, Kim; Fernandez, Anne-Marie; Abarca-Quinones, Jorge; Baurain, Roger; Lobl, Thomas J.; Oliyai, Cecilia; Shochat, Dan; Dubois, Vincent
CORPORATE SOURCE: Laboratory of Cell Biology, Universite Catholique de Louvain, Louvain-la-Neuve, B-1348, Belg.
SOURCE: Cancer Research (2001), 61(7), 2843-2846
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Oligopeptidic derivs. of anthracyclines unable to penetrate cells were prepared and screened for their stability in human blood and their reactivation by peptidases secreted by cancer cells. N-β-alanyl-L-leucyl-L-alanyl-L-leucyl-doxorubicin was selected as a new candidate prodrug. The NH2-terminal β-alanine allows a very good blood stability. A two-step activation by peptidases found in conditioned media of cancer cells ultimately yields N-L-leucyl-doxorubicin. In vitro, when MCF-7/6 cancer cells are exposed to the prodrug, they accumulate about 14 times more doxorubicin than MRC-5 normal fibroblasts, whereas when exposed to doxorubicin the uptake is slightly higher in fibroblasts than in MCF-7/6 cells. This increased specificity of the prodrug over doxorubicin was confirmed in cytotoxicity assays using the same cell types. In vivo, the prodrug proved about nine times less toxic than doxorubicin in the normal mouse and also much more efficient in two different exptl. chemotherapy models of human breast tumors.

IT 177953-54-7
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(extracellularly tumor-activated prodrugs for selective chemotherapy of cancer and application to doxorubicin and preliminary in vitro and in vivo studies in relation to toxicity)

RN 177953-54-7 HCAPLUS
CN 5,12-Naphthacenedione, 10-[[3-[(L-alanyl-L-leucyl)amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, (8S,10S)- (CA INDEX NAME)

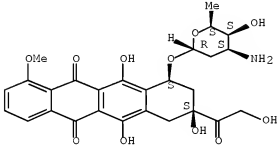
Absolute stereochemistry.



IT 23214-92-8D, Doxorubicin, peptide prodrugs 177953-52-5
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(extracellularly tumor-activated prodrugs for selective chemotherapy of cancer and application to doxorubicin and preliminary in vitro and in vivo studies in relation to toxicity)

RN 23214-92-8 HCAPLUS
CN 5,12-Naphthacenedione, 10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, (8S,10S)- (CA INDEX NAME)

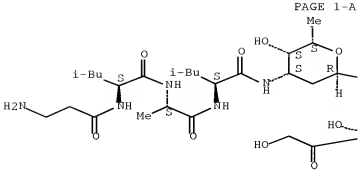
Absolute stereochemistry.



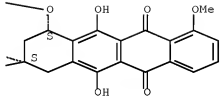
RN 177953-52-5 HCAPLUS
CN 5,12-Naphthacenedione, 10-[[3-[(β-alanyl-L-leucyl-L-alanyl-L-leucyl)amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 19 OF 20 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2001:202127 HCAPLUS Full-text
TITLE: Sythesis OF CPI-0004Na, a doxorubicin tap prodrug
AUTHOR(S): Gangwar, Sanjeev; Lewis, Evan; Viski, Peter; Lobl, Tom; Trouet, Andre; Van Derpooten, Kim; Dubois, Vincent; Fernandez, A. M.
CORPORATE SOURCE: Dept. of Medicinal Chemistry, Coulter Pharmaceuticals, South San Francisco, CA, 94080, USA
SOURCE: Abstracts of Papers, 221st ACS National Meeting, San Diego, CA, United States, April 1-5, 2001 (2001) MEDI-223
CODEN: 69FZD4
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal; Meeting Abstract
LANGUAGE: English

AB Many anti-tumor agents such as anthracyclines and vinca alkaloids have been developed in the last few years that are especially effective for the treatment of cancer cells. However, these mols. are often characterized in vivo by acute toxicity, especially marrow and chronic cardiac toxicity in the case of anthracyclines and a chronic neurol. toxicity in the case of the vinca alkaloids. CPI-0004Na is tumor activated peptide (TAP) prodrug of doxorubicin that is stable in blood and activated in the vicinity of tumors. CPI-0004Na is activated selectively in tumors in a MCF7 human tumor xenograft model

thereby increasing its therapeutic index. As a result it can be given at a higher dose than doxorubicin and is effective in doxorubicin resistant tumors. The design and the synthesis of CPI-0004Na, a new TAP anticancer therapeutic, is presented.

L36 ANSWER 20 OF 20 HCAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2000:401690 HCAPLUS Full-text
DOCUMENT NUMBER: 133:48878
TITLE: Oligopeptide prodrug compounds and process for preparation thereof
INVENTOR(S): Lobl, Thomas J.; Dubois, Vincent; Fernandez, Anne-Marie; Gangwar, Sanjeev; Lewis, Evan; Nieder, Matthew H.; Trouet, Andre; Viski, Peter; Yarranton, Geoffrey T.
PATENT ASSIGNEE(S): Coulter Pharmaceutical, Inc., USA
SOURCE: PCT Int. Appl., 125 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000033888	A2	20000615	WO 1999-US30393	19991210
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W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2354766	A1	20000615	CA 1999-2354766	19991210
EP 1144011	A2	20011017	EP 1999-967462	19991210
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JP 2003518000	T	20030603	JP 2000-586378	19991210
AU 773420	B2	20040527	AU 2000-23733	19991210
NZ 512171	A	20040730	NZ 1999-512171	19991210
IL 143666	A	20090211	IL 1999-143666	19991210
US 20020142955	A1	20021003	US 2001-879442	20010611
US 7425541	B2	20080916		
PRIORITY APPLN. INFO.:			US 1998-111793P P	19981211
			US 1999-119312P P	19990208
			WO 1999-US30393 W	19991210
			US 2000-211887P P	20000614
			US 2001-290448P P	20010511

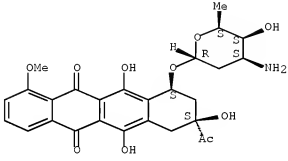
OTHER SOURCE(S): MARPAT 133:48878
AB The prodrug of the invention is a modified form of a therapeutic agent and comprises a therapeutic agent, an oligopeptide, a stabilizing group and, optionally, a linker group. The prodrug is cleavable by the enzyme trouase. Also disclosed are processes for making the prodrug compds.
IT 20830-81-3, Daunorubicin 23214-92-8, Doxorubicin
RL: BAC (Biological activity or effector, except adverse); BPR (Biological

process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(oligopeptide prodrug compds. and process for preparation thereof)

RN 20830-81-3 HCAPLUS

CN 5,12-Naphthacenedione, 8-acetyl-10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S,10S)- (CA INDEX NAME)

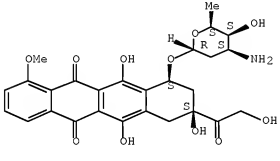
Absolute stereochemistry.



RN 23214-92-8 HCAPLUS

CN 5,12-Naphthacenedione, 10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.



IT 177953-52-5 274912-87-7 274912-88-8
274912-89-9 274912-90-2 274912-91-3
274912-92-4 274912-99-1 274913-00-7
274913-01-8 274913-02-9 274913-03-0
274913-06-3 274913-07-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oligopeptide prodrug compds. and process for preparation thereof)

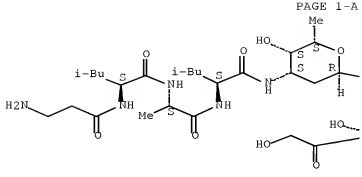
RN 177953-52-5 HCAPLUS

CN 5,12-Naphthacenedione, 10-[[3-[(β-alanyl-L-leucyl-L-alanyl-L-leucyl)amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, (8S,10S)- (9CI)

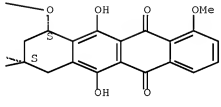
(CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

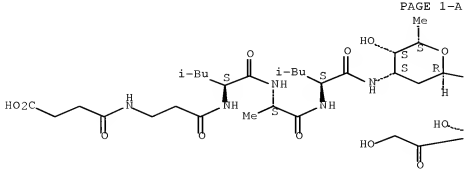


RN 274912-87-7 HCAPLUS

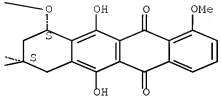
CN 5,12-Naphthacenedione, 10-[[3-[[N-(3-carboxy-1-oxopropyl)-β-alanyl-L-leucyl-L-alanyl-L-leucyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-, (8S,10S)- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

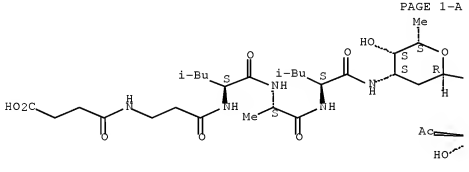


RN 274912-88-8 HCAPLUS

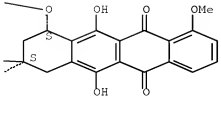
CN 5,12-Naphthacenedione, 8-acetyl-10-[[3-[[N-(3-carboxy-1-oxopropyl)-β-alanyl-L-leucyl-L-alanyl-L-leucyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

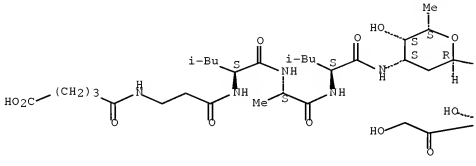


RN 274912-89-9 HCAPLUS

CN 5,12-Naphthacenedione, 10-[[3-[[N-(4-carboxy-1-oxobutyl)-β-alanyl-L-leucyl-L-alanyl-L-leucyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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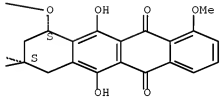
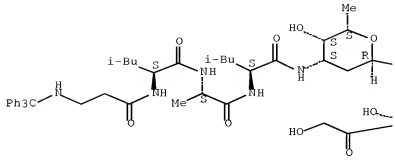


RN 274912-90-2 HCAPLUS

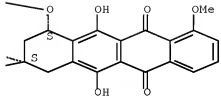
CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[[N-(triphenylmethyl)-β-alanyl-L-leucyl-L-alanyl-L-leucyl]amino]-α-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



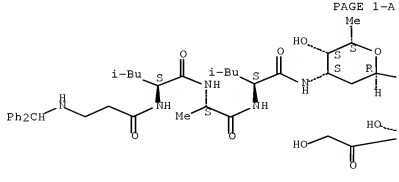
PAGE 1-B



RN 274912-91-3 HCAPLUS
CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[[N-(diphenylmethyl)-β-alanyl-L-leucyl-L-alanyl-L-leucyl]amino]-α-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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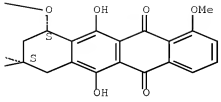
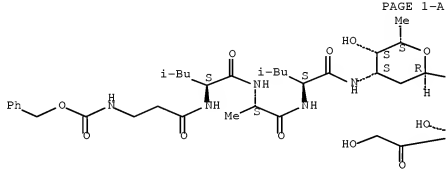


RN 274912-92-4 HCAPLUS
CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[[N-[(phenylmethoxy)carbonyl]-β-alanyl-L-leucyl-L-alanyl-L-leucyl]amino]-α-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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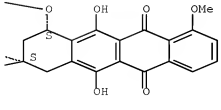

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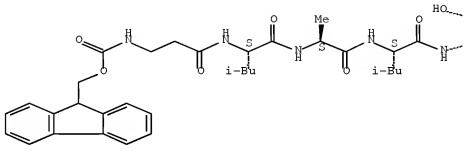
CN 5,12-Naphthacenedione, 8-acetyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-10-[[2,3,6-trideoxy-3-[[N-[(9H-fluoren-9-ylmethoxy)carbonyl]-

β-alanyl-L-leucyl-L-alanyl-L-leucyl]amino]-α-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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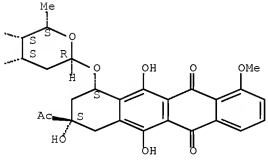
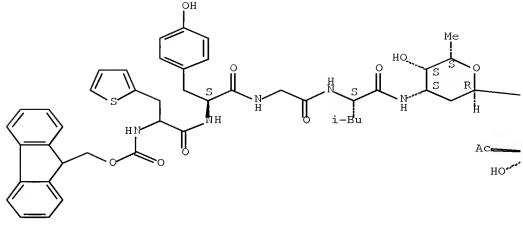


RN 274913-00-7 HCAPLUS

CN 5,12-Naphthacenedione, 8-acetyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-10-[[2,3,6-trideoxy-3-[[N-[(9H-fluoren-9-ylmethoxy)carbonyl]-3-(2-thienyl)alanyl-L-tyrosylglycyl-L-leucyl]amino]-α-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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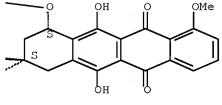
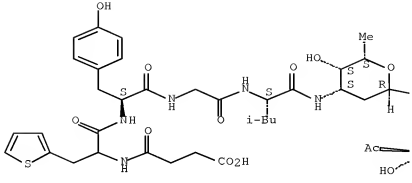


RN 274913-01-8 HCAPLUS
CN 5,12-Naphthacenedione, 8-acetyl-10-[[3-[[N-(3-carboxy-1-oxopropyl)-3-(2-thienyl)alanyl-L-tyrosylglycyl-L-leucyl]amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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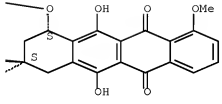


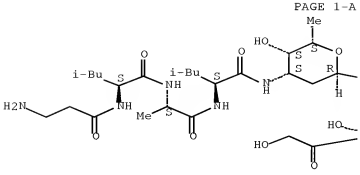
RN 274913-02-9 HCAPLUS
CN Propanoic acid, 2-hydroxy-, compd. with (8S,10S)-10-[[3-[(β-alanyl-L-leucyl-L-alanyl-L-leucyl)amino]-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl]oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-5,12-naphthacenedione (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 177953-52-5
CMF C45 H61 N5 O15

Absolute stereochemistry.

PAGE 1-A



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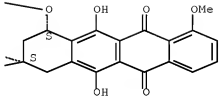

CM 2

CRN 50-21-5
CMF C3 H6 O3

RN 274913-03-0 HCAPLUS
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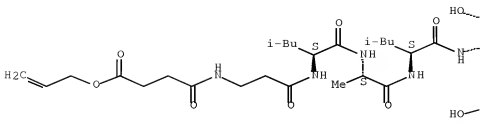
Absolute stereochemistry.

PAGE 1-A



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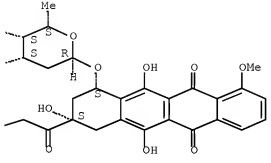
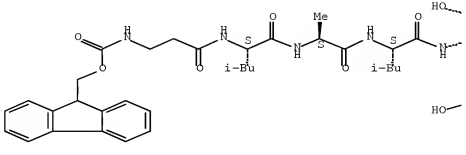


RN 274913-06-3 HCAPLUS
CN 5,12-Naphthacenedione, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-10-[[2,3,6-trideoxy-3-[[N-[(9H-fluoren-9-ylmethoxy)carbonyl]-β-alanyl-L-leucyl-L-alanyl-L-leucyl]amino]-α-L-lyxo-hexopyranosyl]oxy]-, (8S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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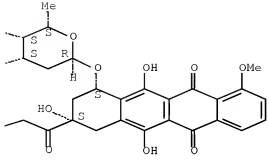

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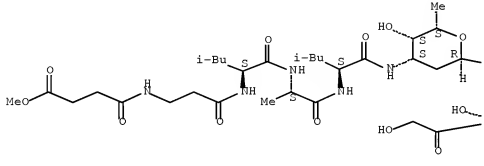
Absolute stereochemistry.

PAGE 1-A



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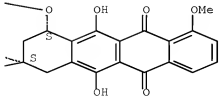

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L29            10 SEA ABB=ON  PLU=ON  L20 NOT (L28 OR L13)
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